

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/27103 A1(51) International Patent Classification⁷: C07D 401/12,
405/12, 209/14, 215/38, 221/02, 265/36, 498/02, 471/02,
A61K 31/495, 31/381, 31/4436, 31/4439, 31/47, 31/506,
31/5365

(21) International Application Number: PCT/US00/27844

(22) International Filing Date: 6 October 2000 (06.10.2000)

(25) Filing Language: English

(26) Publication Language: English

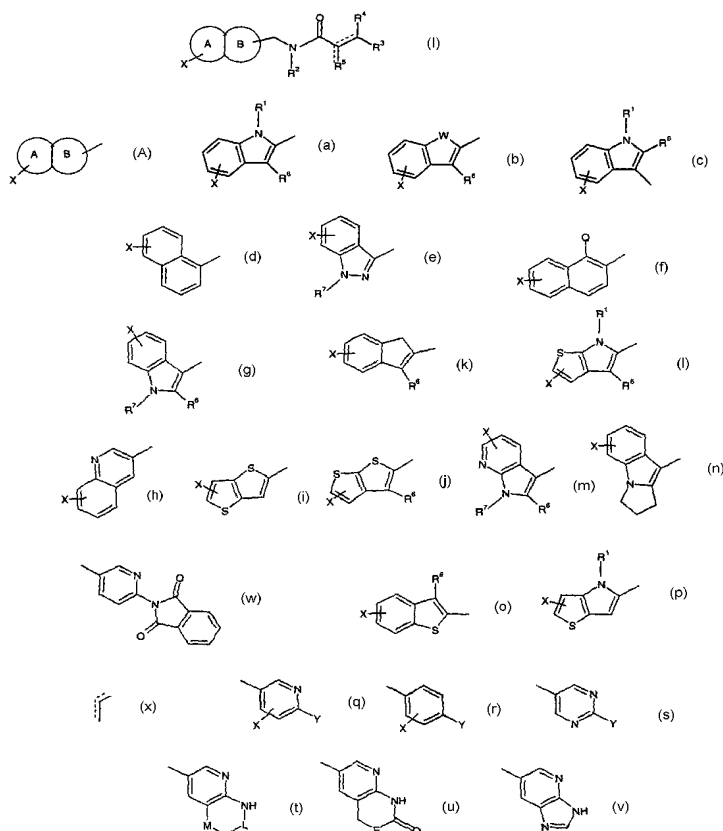
(30) Priority Data:
60/158,704 8 October 1999 (08.10.1999) US(71) Applicant (for all designated States except US):
SMITHKLINE BEECHAM CORPORATION
[GB/GB]; One Franklin Plaza, Philadelphia, PA 19103
(GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): MILLER, William,
H. [US/US]; 132 Chinaberry Lane, Collegeville, PA 19426
(US). NEWLANDER, Kenneth, A. [US/US]; 911 Sage
Road, West Chester, PA 19382 (US). SEEFELD, Mark,
A. [US/US]; 2015 Waterfall Circle, Collegeville, PA 19426
(US). UZINSKAS, Irene, N. [US/US]; 154 Vassar Circle,
Villanova, PA 19085 (US). DeWOLF, Walter, E., Jr.
[US/US]; 64 Glen Manor Lane, Glenmoore, PA 19343
(US). JAKAS, Dalia, R. [US/US]; 528 Lexington Lane,
Norristown, PA 19403 (US).(74) Agents: McCARTHY, Mary, E. et al.; SmithKline
Beecham Corporation, Corporate Intellectual Property,
UW 2220, 709 Swedeland Road, P.O. Box 1539, King of
Prussia, PA 19406-0939 (US).(81) Designated States (national): AE, AL, AU, BA, BB, BG,
BR, BZ, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID,

[Continued on next page]

(54) Title: FAB I INHIBITORS



(57) Abstract: Compounds of formula (I) are disclosed which are Fab I inhibitors and are useful in the treatment of bacterial infections. In said formula, (A) is (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m), (n), (o) or (p); (I) wherein R¹ is H or C₁₋₄alkyl; R² is H, C₁₋₄alkyl or C₃₋₆cycloalkyl; R³ is (q), (r), (s), (t), (u), (v) or (w); R⁴ is H or C₁₋₄alkyl; (x) indicates that one of the two designated bonds is a double bond and the other is a single bond; R⁵ is CH₂ when the bond to which it is attached is a double bond; or R⁵ is H or C₁₋₄alkyl when the bond to which it is attached is a single bond; R⁶ is H or C₁₋₄alkyl; R⁷ is H, C₁₋₆alkyl or -C₀₋₆alkyl-Ar; Y is H, C₁₋₄alkyl, N(R')₂, NHC(O)R', NHCH₂C(O)R' or NHC(O)CH=CHR'; each X independently is H, C₁₋₄alkyl, CH₂OH, OR', SR', CN, N(R')₂, CH₂N(R')₂, NO₂, CF₃, CO₂R', CON(R')₂, COR', NR'C(O)R', F, Cl, Br, I or -S(O)_rCF₃; W is S or O, Q is H or C₁₋₄alkyl; M is CH₂ or O; L is CH₂ or C(O); E is O or NR'; each R' independently is H, C₁₋₆alkyl or -C₀₋₆alkyl-Ar; and r is 0, 1 or 2; or a pharmaceutically acceptable salt thereof.



IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE

Fab I Inhibitors

FIELD OF THE INVENTION

5 This invention relates to pharmaceutically active compounds which inhibit Fab I and are useful for the treatment of bacterial infections.

BACKGROUND OF THE INVENTION

10 While the overall pathway of saturated fatty acid biosynthesis is similar in all organisms, the fatty acid synthase (FAS) systems vary considerably with respect to their structural organization. Vertebrates and yeast possess a FAS in which all the enzymatic activities are encoded on one or two polypeptide chains, respectively, and the acyl carrier protein (ACP) is an integral part of the complex. In contrast, in bacterial FAS, each of the reactions is catalyzed by a distinct, mono-functional enzyme and the ACP is a discrete
15 protein. Therefore, there is considerable potential for the selective inhibition of the bacterial system by antibacterial agents.

 Fab I (previously designated EnvM) functions as an enoyl-ACP reductase (Bergler, et al, (1994), *J.Biol.Chem.* 269, 5493-5496) in the final step of the four reactions involved in each cycle of bacterial fatty acid biosynthesis. In this pathway, the first step is catalyzed
20 by β -ketoacyl-ACP synthase, which condenses malonyl-ACP with acetyl-CoA (FabH, synthase III). In subsequent rounds, malonyl-ACP is condensed with the growing-chain acyl-ACP (FabB and FabF, synthases I and II, respectively). The second step in the elongation cycle is ketoester reduction by NADPH-dependent β -ketoacyl-ACP reductase (FabG). Subsequent dehydration by β -hydroxyacyl-ACP dehydrase (either FabA or FabZ)
25 leads to trans-2-enoyl-ACP, which in turn is converted to acyl-ACP by NADH-dependent enoyl-ACP reductase (Fab I). Further rounds of this cycle, adding two carbon atoms per cycle, eventually lead to palmitoyl-ACP (16C), where upon the cycle is stopped largely due to feedback inhibition of Fab I by palmitoyl-ACP (Heath, et al, (1996), *J.Biol.Chem.* 271, 1833-1836). Thus, Fab I is a major biosynthetic enzyme and is a key regulatory point in the
30 overall synthetic pathway of bacterial fatty acid biosynthesis. Therefore, Fab I is an ideal target for antibacterial intervention.

 Studies have shown that diazaborine antibiotics inhibit fatty acid, phospholipid and lipopolysaccharide (LPS) biosynthesis and that the antibacterial target of these compounds is Fab I. For example, derivative 2b18 from Grassberger, et al, (1984) *J. Med Chem* 27,
35 947-953 has been reported to be a non-competitive inhibitor of Fab I (Bergler, et al, (1994) *J.Biol.Chem.* 269, 5493-5496). Also, plasmids containing the Fab I gene from diazaborine

resistant *S. typhimurium* conferred diazaborine resistance in *E. coli* (Turnowsky, et al, (1989) *J. Bacteriol.*, 171, 6555-6565). Furthermore, inhibition of Fab I either by diazaborine or by raising the temperature in a Fab I temperature sensitive mutant is lethal. These results demonstrate that Fab I is essential to the survival of the organism (Bergler, et al, (1994) *J. Biol. Chem.* 269, 5493-5496).

Recent studies have shown that Fab I is also the target for the broad spectrum antibacterial agent triclosan (McMurry, et al, (1998) *Nature* 394, 531-532). A crystal structure of the *E. Coli* Fab I complexed with NAD and triclosan shows that triclosan acts as a site-directed, very potent inhibitor of Fab I by mimicking its natural substrate (Levy, et al, (1999) *Nature* 398, 383-384). Ward, et al ((1999) *Biochem.* 38, 12514-12525) have shown that there is no evidence for the formation of a covalent complex between Fab I and triclosan, which would be analogous to the diazaborines; triclosan differs from these compounds in that it is a reversible inhibitor of Fab I. The structural data for the complex of Fab I with NAD and triclosan provides important information about Fab I as a therapeutic target.

Importantly, it has now been discovered that certain compounds are Fab I inhibitors and have antibacterial activity, and, therefore, may be useful for the treatment of bacterial infections in mammals, particularly in man.

Additionally, two of the instant Fab I inhibiting compounds have been found to be inhibitors of Streptococcus Fab K. Fab I is not present in Streptococcus, and is not essential in Pseudomonas. There is also reason to believe that Fab I may not be essential in Enterococcus. In all of these organisms, another enoyl reductase, termed Fab K, is present (Heath, R. J.; Rock, C.O., *Nature* (2000), 406, 145-146). Pseudomonas and Enterococcus contain both Fab I and Fab K, and Streptococcus contains only Fab K. Consequently, pure Fab I inhibitors are not expected to have antibacterial activity in these organisms. Thus, compounds that inhibit both Fab I and Fab K have the potential to be broad-spectrum antibacterial agents.

SUMMARY OF THE INVENTION

This invention comprises compounds of the formula (I), as described hereinafter, which inhibit Fab I and are useful in the treatment of bacterial infections.

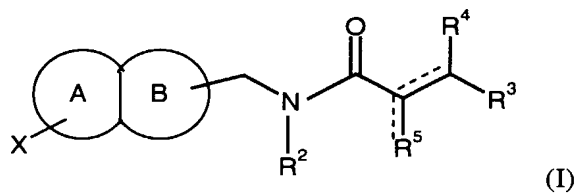
This invention is also a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically acceptable carrier.

This invention is a method of treating bacterial infections by inhibiting Fab I and, for certain compounds, also inhibiting Fab K. In a particular aspect, the compounds of this invention are useful as antibacterial agents.

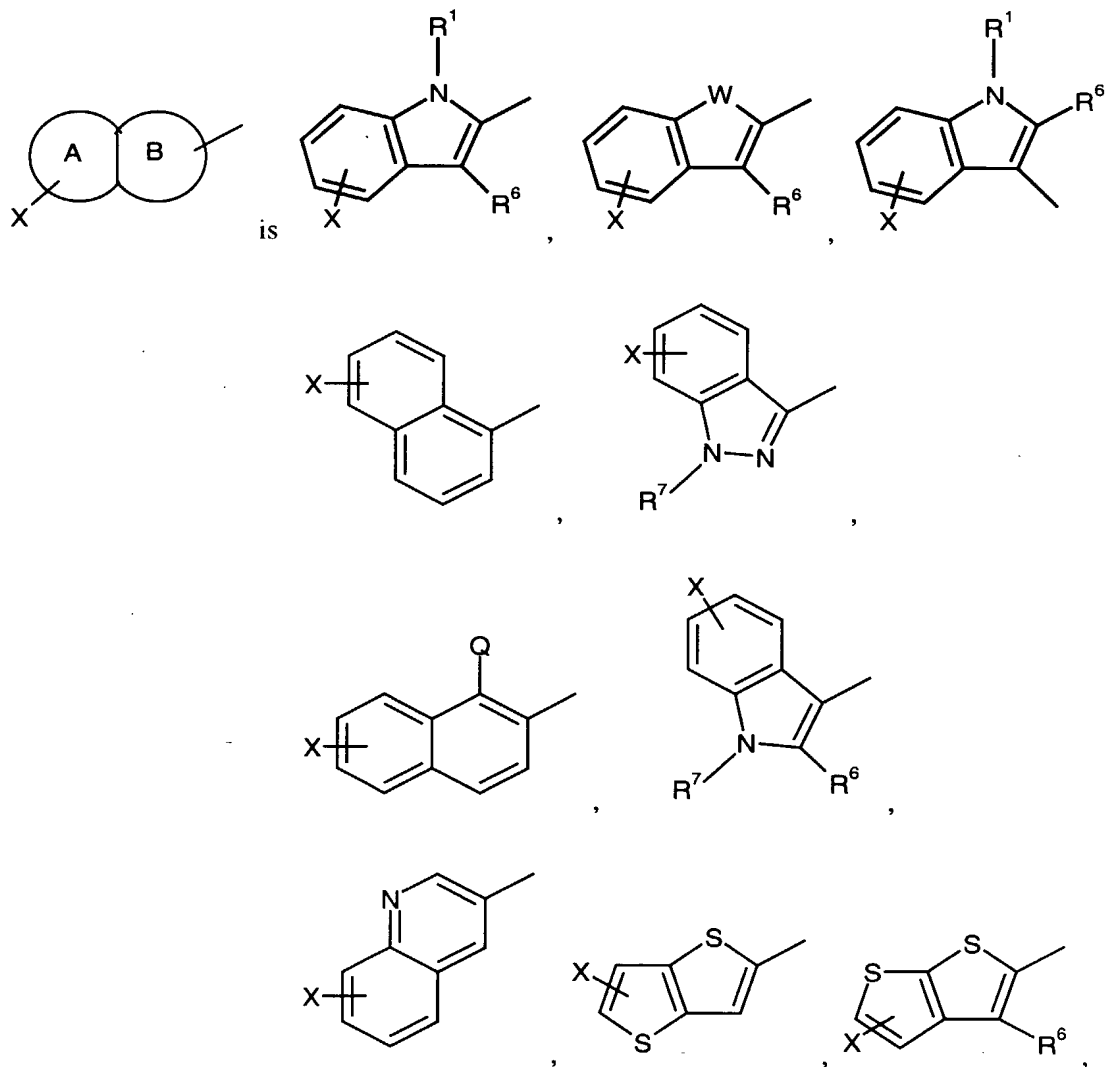
This invention also comprises the preparation and purification of crotonoyl-ACP and the use of this purified enzyme in a Fab I enzyme inhibition assay.

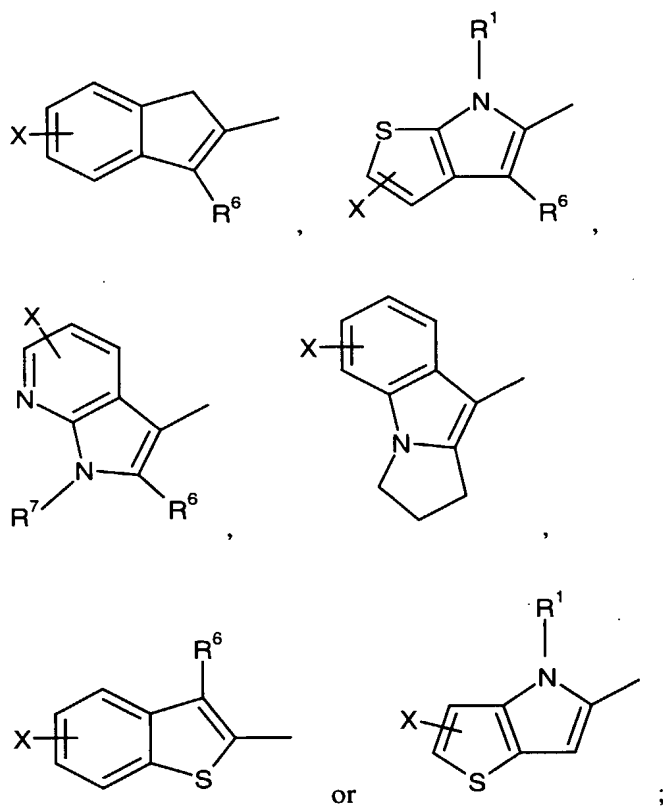
DETAILED DESCRIPTION

5 This invention comprises compounds of formula (I):



wherein:



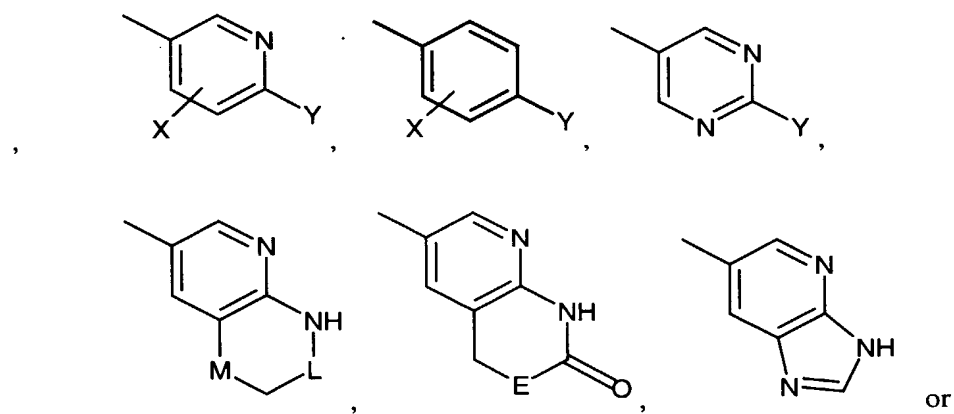


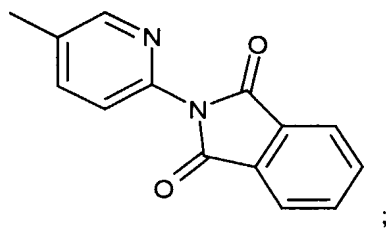
R^1 is H or C_{1-4} alkyl;

R^2 is H, C_{1-4} alkyl or C_{3-6} cycloalkyl;

R^3 is

10





R^4 is H or C_{1-4} alkyl;





indicates that one of the two designated bonds is a double bond and the other is a single bond;

- 5 R^5 is CH_2 when the bond to which it is attached is a double bond; or R^5 is H or C_{1-4} alkyl when the bond to which it is attached is a single bond;
 R^6 is H or C_{1-4} alkyl;
 R^7 is H, C_{1-6} alkyl or $-C_{0-6}$ alkyl-Ar;
Y is H, C_{1-4} alkyl, $N(R')_2$, $NHC(O)R'$, $NHCH_2C(O)R'$ or $NHC(O)CH=CHR'$;
10 each X independently is H, C_{1-4} alkyl, CH_2OH , OR' , SR' , CN , $N(R')_2$, $CH_2N(R')_2$, NO_2 , CF_3 , CO_2R' , $CON(R')_2$, COR' , $NR'C(O)R'$, F, Cl, Br, I or $-S(O)_rCF_3$;
W is S or O;
Q is H or C_{1-4} alkyl;
M is CH_2 or O;
15 L is CH_2 or $C(O)$;
E is O or NR' ;
each R' independently is H, C_{1-6} alkyl or $-C_{0-6}$ alkyl-Ar; and
r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

- 20 Also included in this invention are pharmaceutically acceptable addition salts and complexes of the compounds of this invention. In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique racemic compound, as well as each unique nonracemic compound.

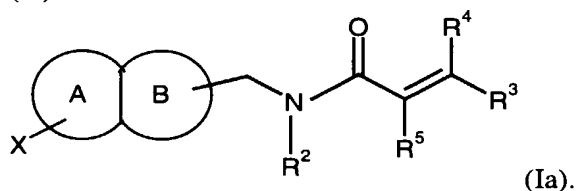
- In cases in which compounds have unsaturated carbon-carbon double bonds, both
25 the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, such as 
and , each tautomeric form is contemplated as being included within this invention, whether existing in equilibrium or locked in one form by appropriate substitution with R' .

The meaning of any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence.

Also included in this invention are prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*.

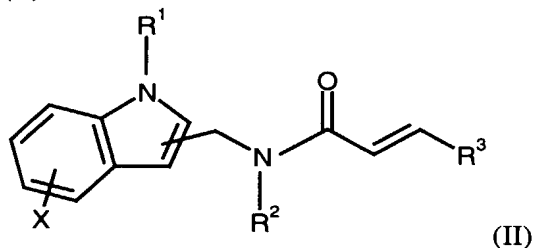
The compounds of formula (I) inhibit Fab I. Inhibition of this enzyme is useful in the treatment of bacterial infections. Also, the compounds of this invention may be useful as antifungal agents. Additionally, the compounds may be useful in combination with known antibiotics.

With respect to formula (I), this invention preferably includes compounds of formula (Ia):



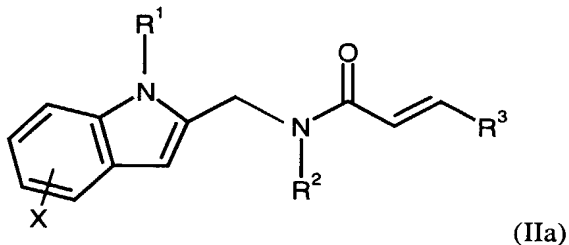
in which R^2 , R^3 , R^4 , R^5 and X are as defined for formula (I) compounds.

With respect to formula (I), this invention preferably includes compounds of formula (II):



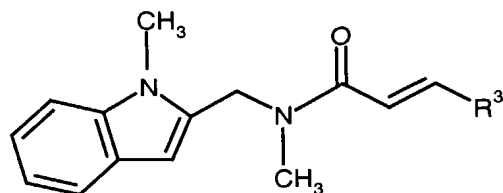
in which R^1 , R^2 , R^3 and X are as defined for formula (I) compounds.

With respect to formula (II), this invention preferably includes compounds of formula (IIa):



in which R^1 , R^2 , R^3 and X are as defined for formula (I) compounds.

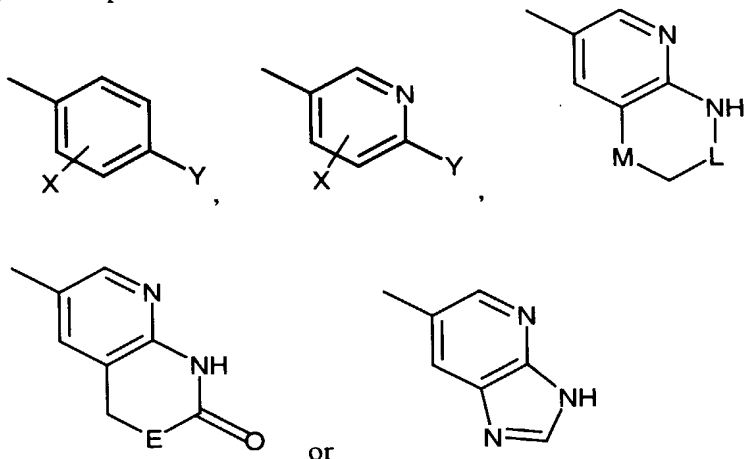
In particular, with respect to formula (II), this invention preferably includes compounds of formula (IIb):



(IIb)

in which R^3 is as defined for formula (I) compounds.

5 Suitably, with respect to formula (I), R^3 is:



in which X, Y, M, L and E are as defined for formula (I) compounds.

10 Representative of the novel compounds of this invention are the compounds of examples 1-86 hereinafter. The compounds of this invention are Fab I inhibitors useful in the treatment of bacterial infections. Two compounds of this invention, namely (E)-N-methyl-N-(1-methyl-1H-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide and (E)-N-methyl-N-(2-methyl-1H-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide, are dual Fab I/Fab K inhibitors. These
15 compounds have the potential to be broad spectrum antibiotics.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of this invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as
20 described in *Eur. J. Biochem.*, 158, 9 (1984).

C_{1-4} alkyl as applied herein means an optionally substituted alkyl group of 1 to 4 carbon atoms, and includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. C_{1-6} alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C_{0-4} alkyl and C_{0-6} alkyl additionally indicates that no
25 alkyl group need be present (e.g., that a covalent bond is present).

Any C₁₋₄alkyl or C₁₋₆ alkyl may be optionally substituted with the group R^x, which may be on any carbon atom that results in a stable structure and is available by conventional synthetic techniques. Suitable groups for R^x are C₁₋₄alkyl, OR', SR', CN, N(R')₂, CH₂N(R')₂, -NO₂, -CF₃, -CO₂R', -CON(R')₂, -COR', -NR'C(O)R', F, Cl, Br, I, or
5 -S(O)_rCF₃, wherein R' and r are as defined for formula (I) compounds.

Halogen or halo means F, Cl, Br, and I.

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to three substituents, such as those defined above for alkyl, or substituted by methylenedioxy.

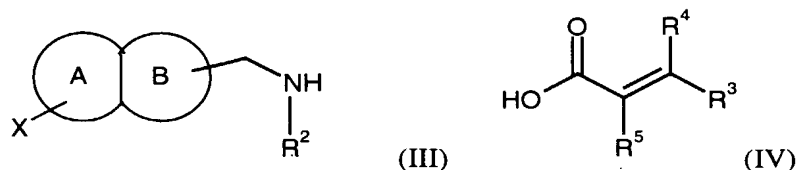
10 Het, or heterocycle, indicates an optionally substituted five or six membered monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable and available by conventional chemical synthesis. Illustrative heterocycles are benzofuryl, benzimidazolyl, benzopyranyl, benzothienyl, furyl, imidazolyl, indolyl, morpholyl,
15 piperidyl, piperazyl, pyrrolyl, pyrrolidinyl, tetrahydropyridyl, pyridyl, thiazolyl, thienyl, quinolyl, isoquinolyl, and tetra- and perhydro- quinolyl and isoquinolyl. Any accessible combination of up to three substituents on the Het ring, such as those defined above for alkyl, that are available by chemical synthesis and are stable are within the scope of this invention.

20 Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical, Bn refers to the benzyl radical, Me refers to methyl, Et refers to ethyl, Ac refers to acetyl, Alk refers to C₁₋₄alkyl, Nph refers to 1- or 2-naphthyl and cHex
25 refers to cyclohexyl. Tet refers to 5-tetrazolyl.

Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, EDC refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride, HOBt refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DEAD refers to diethyl
30 azodicarboxylate, PPh₃ refers to triphenylphosphine, DIAD refers to diisopropyl azodicarboxylate, DME refers to dimethoxyethane, DMF refers to dimethylformamide, NBS refers to N-bromosuccinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to polyphosphoric acid, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate, HF refers to
35 hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

Generally, compounds of this invention are prepared by:

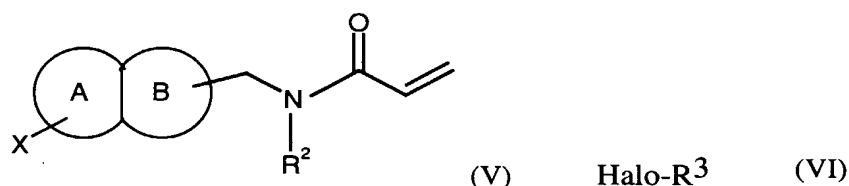
(i) reacting a compound of formula (III) with a compound of formula (IV):



5

wherein R^2 , R^3 , R^4 , R^5 and X are as defined in formula (I), with any reactive functional groups protected, in the presence of EDC and HOBT;

(ii) reacting a compound of formula (V) with a compound of formula (VI):



10

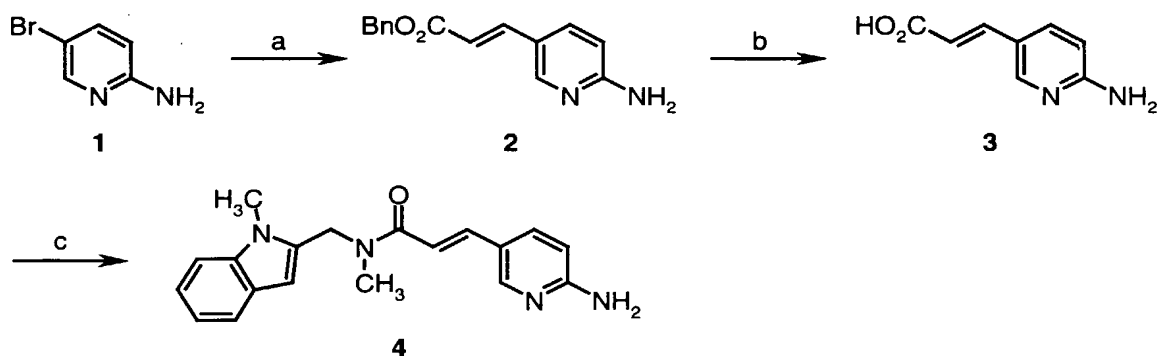
wherein R^2 , R^3 and X are as defined in formula (I) and Halo is Br, Cl, F or I, with any reactive functional groups protected, in the presence of a palladium (II) salt, a phosphine ligand and base;

15 and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

In particular, compounds of the formula (I) are prepared by the general methods described in the Schemes hereinafter.

Scheme I

20



(a) benzyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(\text{o-tol})_3$, $(i\text{-Pr})_2\text{NEt}$, propionitrile; (b) 1.0 N NaOH, MeOH; (c) 1-methyl-2-(methylaminomethyl)indole, EDC, $\text{HOBt} \cdot \text{H}_2\text{O}$, Et_3N , DMF.

A suitable haloaromatic derivative, for instance for instance 2-amino-5-bromopyridine (**I-1**), reacts with an appropriate α,β -unsaturated ester, for example benzyl acrylate, in a Heck-type reaction (see Heck, *Org. Reactions* **1982**, 27, 345) to afford **I-2**.

5 The reaction is mediated by a palladium(0) species, and generally is conducted in an inert solvent, such as CH_3CN , propionitrile, or toluene, in the presence of an appropriate acid scavenger, such as triethylamine (Et_3N) or diisopropylethylamine ($(i\text{-Pr})_2\text{NEt}$). Typical sources of the palladium(0) species include palladium (II) acetate ($\text{Pd}(\text{OAc})_2$) and palladium(II) chloride (PdCl_2), and oftentimes phosphine ligands, for instance
10 triphenylphosphine (PPh_3) or tri-ortho-tolylphosphine ($\text{P}(\text{tol})_3$), are included. The ethyl ester of **I-2** is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl , to afford the carboxylic acid **I-3**. The carboxylic acid of **I-3** is converted to an activated form using, for example, EDC and HOBT, or SOCl_2 ,
15 and the activated form is subsequently reacted with an appropriate amine, for instance 1-methyl-2-(methylaminomethyl)indole, in a suitable solvent such as DMF, CH_2Cl_2 , or CH_3CN , to afford **I-4**. Depending on whether acid neutralization is required, an added base, such as triethylamine (Et_3N), diisopropylethylamine ($(i\text{-Pr})_2\text{NEt}$), or pyridine, may be used.

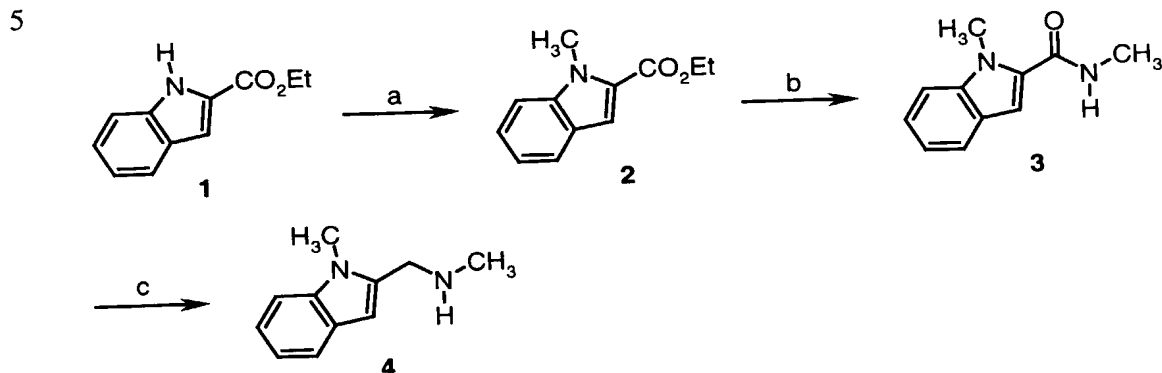
20 Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag), which are incorporated herein by reference.

25 Amide coupling reagents as used herein denote reagents which may be used to form peptide bonds. Typical coupling methods employ carbodiimides, activated anhydrides and esters and acyl halides. Reagents such as EDC, DCC, DPPA, PPA, BOP reagent, HOBT, N-hydroxysuccinimide and oxalyl chloride are typical.

Typically, the amine is coupled via its free amino group to an appropriate
30 carboxylic acid substrate using a suitable carbodiimide coupling agent, such as N,N'-dicyclohexyl carbodiimide (DCC), optionally in the presence of catalysts such as 1-hydroxybenzotriazole (HOBT) and dimethylamino pyridine (DMAP). Other methods, such as the formation of activated esters, anhydrides or acid halides, of the free carboxyl of a suitably protected acid substrate, and subsequent reaction with the free amine, optionally in
35 the presence of a base, are also suitable. For example, a benzoic acid is treated in an anhydrous solvent, such as methylene chloride or tetrahydrofuran (THF), in the presence of

a base, such as N-methylmorpholine, DMAP or a trialkylamine, with isobutyl chloroformate to form the "activated anhydride", which is subsequently reacted with the free amine.

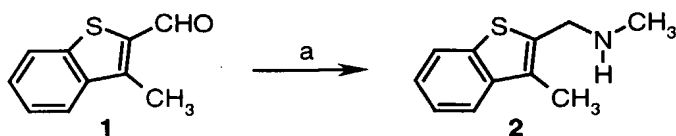
Scheme II



(a) NaH, MeI, DMF; (b) CH₃NH₂, H₂O, MeOH; (c) LiAlH₄, THF.

- 10 The amine coupling partners used in the present invention were prepared by established methods well-known to those of skill in the art. For example, amine **II-4** is prepared by the straightforward procedure outlined in Scheme II. Commercially available ethyl indole-2-carboxylate (**II-1**) is deprotonated with a suitable base, generally sodium hydride (NaH), and the intermediate sodium salt is reacted with an appropriate alkylating agent, for instance methyl iodide, to afford **II-2**. Polar solvents such as DMF, THF, or mixtures thereof are generally preferred for this reaction. Compound **II-2** can be conveniently converted to **II-3** by reaction with an excess of an amine, such as methylamine, in a polar solvent, generally H₂O or a mixture of H₂O and methanol. Alternatively, the ester of **II-2** can be saponified under standard conditions, typically with an alkali metal hydroxide such as LiOH, NaOH, or KOH, in an aqueous solvent, such as THF, ethanol, or methanol, and the resulting carboxylic acid can be converted to the desired amide. Typical methods for forming amides are described in Scheme I. Reduction of the amide **II-3** to the amine **II-4** is typically accomplished with lithium aluminum hydride (LiAlH₄) in refluxing THF, although many other methods can be used to reduce amides to amines. Such methods are well-known to those of skill in the art, and can be found in standard reference volumes, such as "Compendium of Organic Synthetic Methods" (published by Wiley-Interscience).
- 15
- 20
- 25

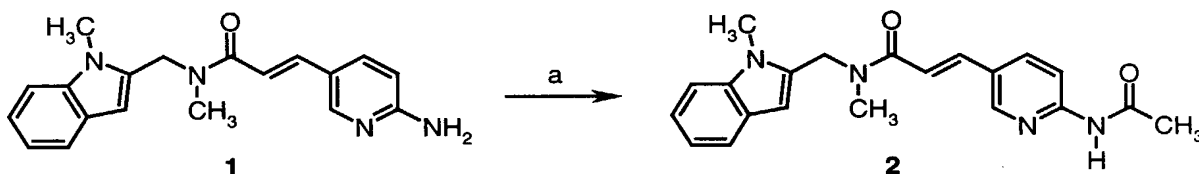
Scheme III



5 (a) CH₃NH₂, NaCNBH₃, MeOH.

The amine coupling partners used in the present invention can also be prepared by the reductive amination of an appropriate aldehyde (Scheme III). This method, which is well-known to those of skill in the art, involves the initial conversion of an aldehyde to an intermediate imine, which is subsequently reduced, oftentimes in situ, to afford the amine. For example, the commercially-available aldehyde **III-1** reacts with an appropriate amine, for instance methylamine, to afford an intermediate imine (not shown), which is reduced in situ to amine **III-2** by reaction with a suitable reducing agent, usually sodium cyanoborohydride or sodium (triacetoxo)borohydride. Frequently, the reaction is conducted in the presence of an acid, such as acetic acid, in a polar solvent such as methanol or DMF.

Scheme IV



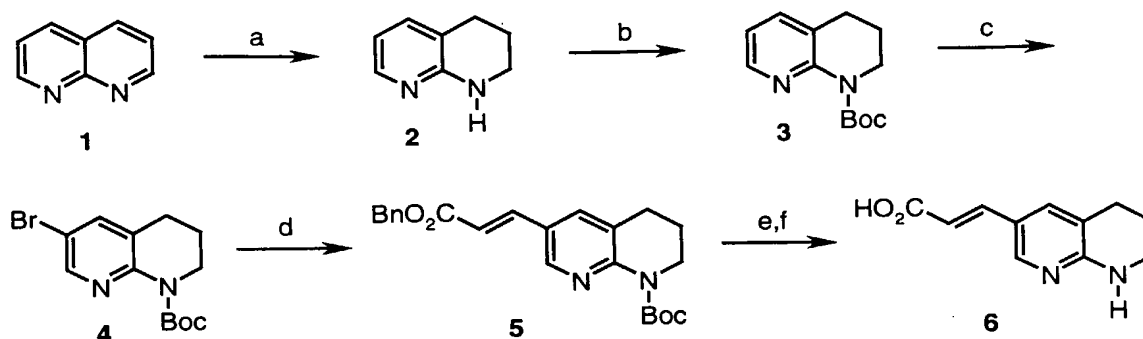
20

(a) Ac₂O, NaHCO₃, THF.

The amine of compound **IV-1** (prepared as described in Scheme I) reacts with a variety of acylating agents to produce amides, sulfonamides, ureas, and carbamates. For example, **IV-1** reacts with acetic anhydride (Ac₂O) in a neutral solvent, typically THF, in the presence of a suitable base, such as sodium bicarbonate (NaHCO₃), to afford **IV-2**. Other acylating agents, including sulfonyl halides, isocyanates, and chlorocarbonates, also participate in this reaction to afford sulfonamides, ureas, and carbamates, respectively.

30

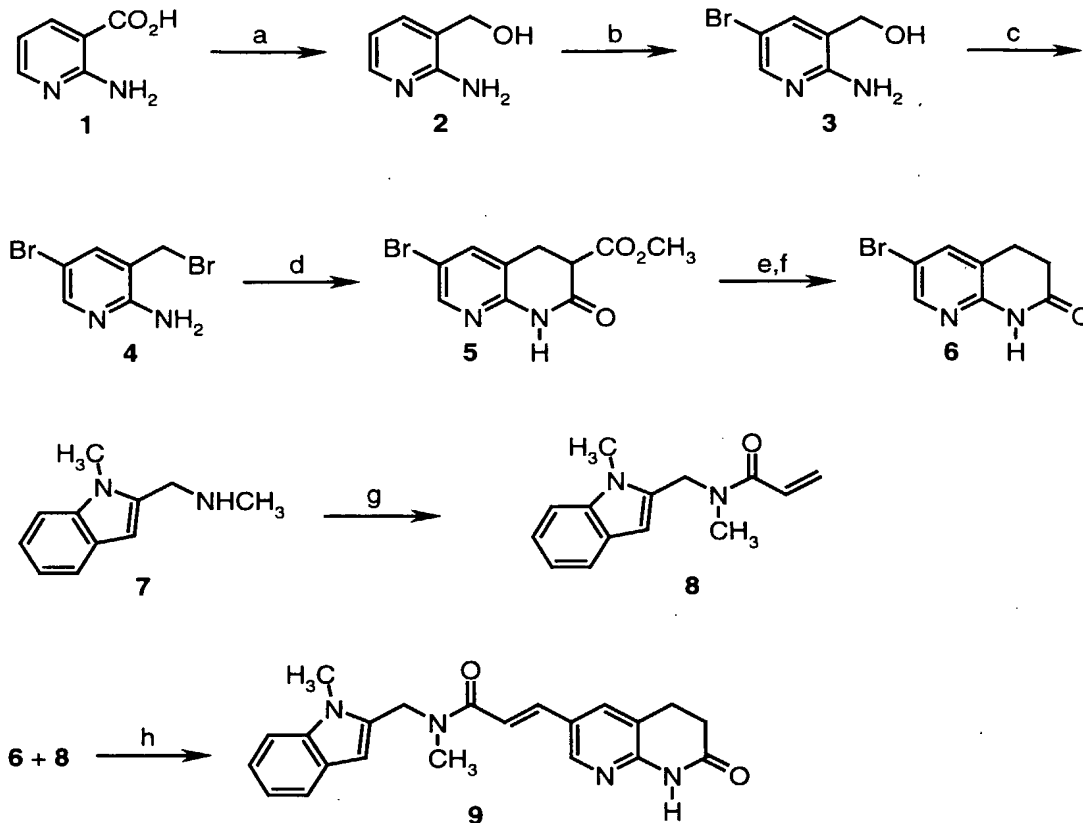
Scheme V



- 5 (a) H_2 , Pd/C, EtOH; (b) $(\text{Boc})_2\text{O}$, LiHMDS, THF; (c) NBS, AcOH, CH_2Cl_2 ; (d) benzyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{NEt}$, propionitrile; (e) 4 N HCl/dioxane; (f) LiOH, H_2O , MeOH.

1,8-Naphthyridine (V-1) can be selectively reduced to 1,2,3,4-tetrahydro-1,8-naphthyridine (V-2) by reaction with hydrogen gas in the presence of a suitable catalyst, preferably palladium metal on activated carbon (Pd/C), in an inert solvent, generally MeOH, EtOH, EtOAc, or mixtures thereof. V-2 is converted to a suitably protected derivative, for instance the N-Boc protected derivative V-3, by reaction with di-*tert*-butyl dicarbonate in the presence of an appropriate base, preferably lithium hexamethyldisilazide (LiHMDS). The protecting group for the amine must be compatible with subsequent chemistry, and must be readily removable when desired. Methods for the protection of amines are well-known to those of skill in the art, and are described in standard reference volumes, such as Greene "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). V-3 is selectively brominated at the 6-position by reaction with a suitable brominating agent, such as bromine (Br_2) or N-bromosuccinimide (NBS). Typical solvents for a bromination reaction include CH_2Cl_2 , CCl_4 , MeOH, AcOH, or mixtures thereof. The resulting 6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridine V-4 participates in a Heck reaction as described in Scheme I to afford V-5. Removal of the Boc protecting group is accomplished under standard acidic conditions well-known to those of skill in the art (see Greene above), and the benzyl ester is saponified as described in Scheme I to afford V-6.

Scheme VI

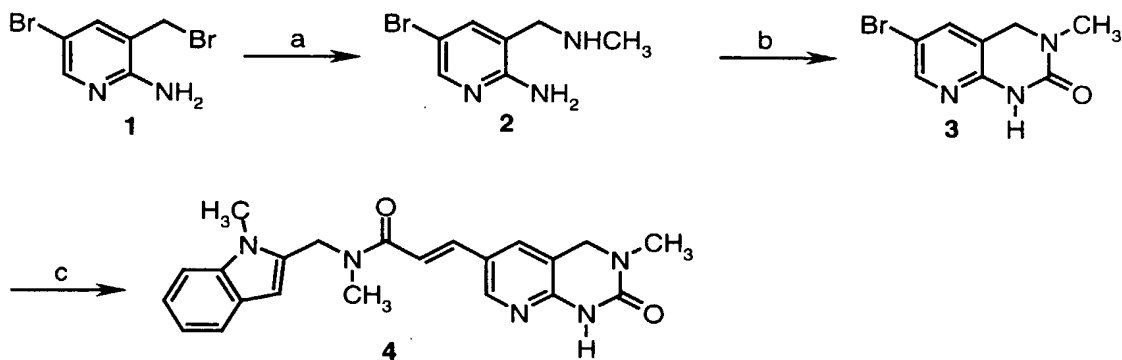


- 5 (a) LiAlH_4 , THF; (b) NBS, CH_2Cl_2 ; (c) 48% HBr; (d) $(\text{MeO}_2\text{C})_2\text{CH}_2$, NaOMe, MeOH; (e) NaOH, H_2O , MeOH, (f) HCl, H_2O , MeOH; (g) acryloyl chloride, Et_3N , CH_2Cl_2 ; (h) $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{NEt}$, propionitrile.

- 10 Commercially available 2-aminonicotinic acid (**VI-1**) is reduced to alcohol **VI-2** under standard conditions (LiAlH_4 , THF), and the aromatic ring of **VI-2** is brominated using, for example, bromine or N-bromosuccinimide (NBS), in a neutral solvent such as CH_2Cl_2 , to afford **VI-3**. On reaction with 48% aqueous HBr, **VI-3** is converted to bromide **VI-4**, which reacts with a diester of malonic acid, for instance dimethyl malonate, in the presence of a suitable base, typically sodium methoxide, in an alcoholic solvent such as methanol, to afford the naphthyridone derivative **VI-5**. Saponification and neutralization under standard conditions affords an intermediate carboxylic acid (not shown), which is typically not isolated, but is subject to decarboxylation on gentle warming to afford the naphthyridone **VI-6**. This compound reacts with acrylamide **VI-8** in a Heck-type reaction
- 15

as described in Scheme I to afford **VI-9**. Alternatively, **VI-6** might be converted to **VI-9** according to the general procedure described in Scheme I for the conversion of **I-1** to **I-4**. The acrylamide **VI-8** is conveniently prepared by reaction of amine **VI-7** (see Scheme II) with an activated form of acrylic acid in an amide bond-forming reaction. Typical conditions for the formation of amides are described in Scheme I, and are well-known to those of skill in the art.

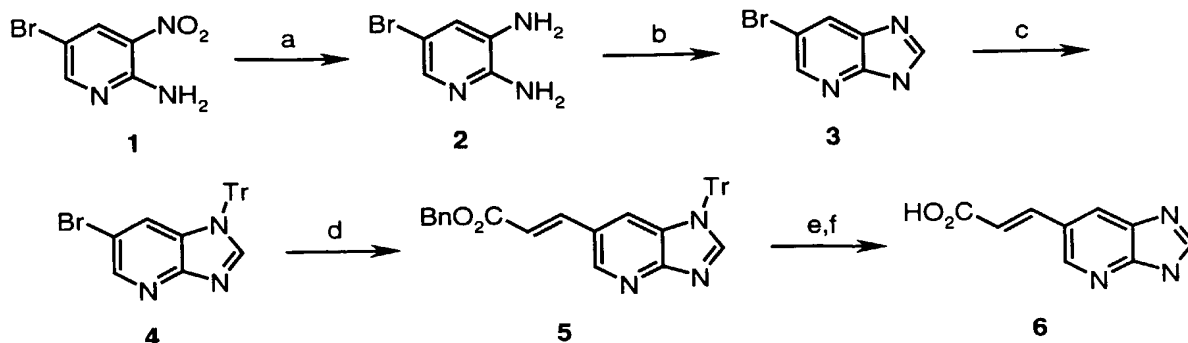
Scheme VII



(a) CH_3NH_2 , H_2O , THF; (b) $(\text{MeO})_2\text{C}=\text{O}$, NaOMe, MeOH; (c) compound **VI-8**, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{NEt}$, propionitrile.

Benzylic bromide **VII-1**, prepared as described in Scheme VI, reacts with an amine, for example aqueous methylamine, to afford benzylic amine **VII-2**. Polar solvents such as THF, DMF, DMSO, or mixture thereof, are generally preferred for this reaction. **VII-2** reacts with a dialkyl carbonate, preferably dimethyl carbonate, in the presence of a suitable base, typically sodium methoxide, in an alcoholic solvent, generally methanol, to afford the cyclic urea derivative **VII-3**. This compound is converted to **VII-4** by reaction with compound **VI-8** as described in Scheme VI.

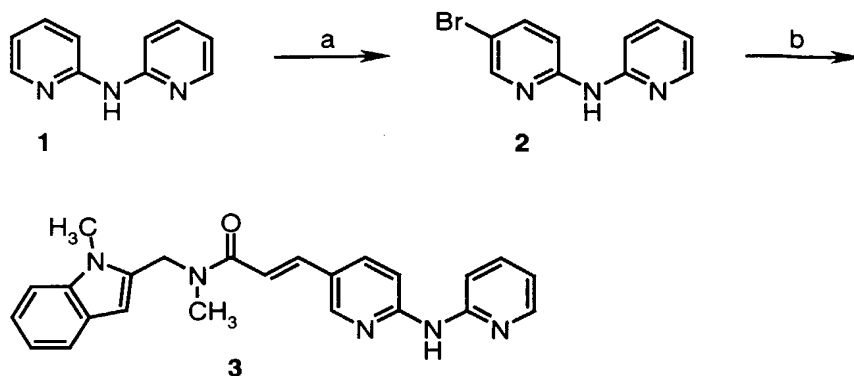
Scheme VIII



- 5 (a) $\text{SnCl}_2 \cdot \text{H}_2\text{O}$, EtOH; (b) 96% HCO_2H ; (c) TrCl , Et_3N , CH_2Cl_2 ; (d) benzyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{NEt}$, propionitrile; (e) 4 N HCl /dioxane; (f) NaOH , H_2O , MeOH .

- 10 The nitro group of commercially available 2-amino-5-bromo-3-nitropyridine (**VIII-1**) is reduced under standard conditions using, for example, tin (II) chloride in EtOH. The resulting diamine, **VIII-2**, reacts with formic acid, or an appropriate equivalent, to afford the imidazopyridine derivative **VIII-3**. This compound is converted to a suitably protected derivative, for instance the N-trityl protected derivative **VIII-4**, by reaction with trityl chloride in the presence of an appropriate base, typically triethylamine or
- 15 diisopropylethylamine. Typical solvents for this reaction include CH_2Cl_2 , DMF, or mixtures thereof. As discussed in Scheme V, the protecting group for the amine must be compatible with the subsequent chemistry, and must be readily removable when desired. **VIII-4** is converted to **VIII-6** according to the general procedure described in Scheme V.

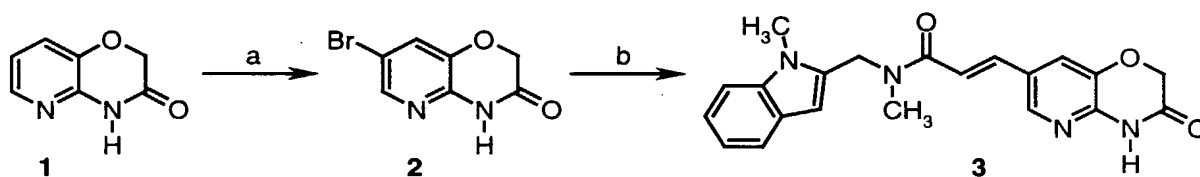
Scheme IX



- 5 (a) Br₂, AcOH; (b) N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide, Pd(OAc)₂, P(o-tol)₃, (i-Pr)₂NEt, propionitrile.

Commercially-available 2,2'-dipyridylamine (**IX-1**) is mono-brominated at the 5-position by reaction with a suitable brominating agent, such as bromine (Br₂) or N-bromosuccinimide (NBS). Typical solvents for a bromination reaction include CH₂Cl₂, CCl₄, MeOH, AcOH, or mixtures thereof. The resulting mono-bromo derivative **IX-2** reacts with N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide in a Heck-type reaction as described in Scheme I to afford **IX-3**.

Scheme X



- 15 (a) Br₂, AcOH; (b) N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide, Pd(OAc)₂, P(o-tol)₃, (i-Pr)₂NEt, propionitrile.

Commercially-available 2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (**X-1**) is selectively brominated at the 5-position by reaction with a suitable brominating agent, such as bromine (Br₂) or N-bromosuccinimide (NBS). Typical solvents for a bromination reaction include CH₂Cl₂, CCl₄, MeOH, AcOH, or mixtures thereof. The resulting mono-bromo derivative **X-2** reacts with N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide in a Heck-type

reaction as described in Scheme I to afford X-3.

Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+ , Na^+ , K^+ , Ca^{++} , Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a compound according to formula (I) and a pharmaceutically acceptable carrier. Accordingly, the compounds of formula (I) may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of formula (I) prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of

a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients, such as cocoa butter, glycerin, gelatin or polyethylene glycols, and molded
5 into a suppository.

For topical administration, the compounds of this invention may be combined with diluents to take the form of ointments, gels, pastes, creams, powders or sprays. The compositions which are ointments, gels, pastes or creams contain diluents, for example, animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives,
10 polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures of these substances. The compositions which are powders or sprays contain diluents, for example, lactose, talc, silicic acid, aluminum hydroxide, calcium silicate and polyamide powder, or mixtures of these substances. Additionally, for topical ophthalmologic administration, the typical carriers are water, mixtures of water and water miscible solvents,
15 such as lower alkanols or vegetable oils, and water-soluble non-toxic polymers, for example cellulose derivatives, such as methyl cellulose.

The compounds described herein are inhibitors of Fab I, and are useful for treating bacterial infections. For instance, these compounds are useful for the treatment of bacterial infections, such as, for example, infections of upper respiratory tract (e.g. otitis media,
20 bacterial tracheitis, acute epiglottitis, thyroiditis), lower respiratory (e.g. empyema, lung abscess), cardiac (e.g. infective endocarditis), gastrointestinal (e.g. secretory diarrhoea, splenic abscess, retroperitoneal abscess), CNS (e.g. cerebral abscess), eye (e.g. blepharitis, conjunctivitis, keratitis, endophthalmitis, preseptal and orbital cellulitis, dacryocystitis), kidney and urinary tract (e.g. epididymitis, intrarenal and perinephric abscess, toxic shock
25 syndrome), skin (e.g. impetigo, folliculitis, cutaneous abscesses, cellulitis, wound infection, bacterial myositis), and bone and joint (e.g. septic arthritis, osteomyelitis). Also, the compounds of this invention may be useful as antifungal agents. Additionally, the compounds may be useful in combination with known antibiotics.

The compounds of this invention are administered to the patient, in a manner such
30 that the concentration of drug is sufficient to treat bacterial infections. The pharmaceutical composition containing the compound is administered at an oral dose of between about 10 mg to about 1000 mg, taken once or several times daily, in a manner consistent with the condition of the patient. Preferably, the oral dose would be about 50 mg to about 500 mg, although the dose may be varied depending upon the age, body weight and symptoms of the
35 patient. For acute therapy, parenteral administration is preferred. An intravenous infusion of the compound of formula (I) in 5% dextrose in water or normal saline, or a similar

formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. The precise level and method by which the compounds are administered is readily determined by one skilled in the art.

5 The compounds may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Cloning of *S. aureus* FabI:

The *fabI* gene was cloned from the chromosomal DNA of *S. aureus* strain
10 WCUH29 using the polymerase chain reaction. Amplification was performed using *Taq* DNA polymerase (BRL) and the following primers: 5'-
CGCCTCGAGATGTTAAATCTTGAAAACAAAACATATGTC-3' and 5'-
CGCGGATCCAATCAAGTCAGGTTGAAATATCCA-3' (*Xho*I and *Bam*HI sites
underlined). The resulting fragment was then digested with *Xho*I and *Bam*HI and ligated
15 into *Xho*I- and *Bam*HI-digested expression vector pET-16b (Novagen), producing pET-His₁₀-*fabI*. The gene sequence of *fabI* was confirmed by automated cycle sequencing using an Applied Biosystems model 377 machine. The untagged version of pET-*fabI* was constructed by digesting pET-His₁₀-*fabI* with *Nco*I and *Nde*I to remove a 97 bp fragment encoding the His 10 tag, the factor Xa cleavage site and the first 8 amino acids of FabI, and
20 replacing it with a linker encoding the first 8 amino acids of FabI plus a glycine residue between the initiator methionine and the lysine at position 2. This plasmid was called pET-*fabI*. The linker was made by annealing the following two oligonucleotides: 5'-
CATGGGCTTAAATCTTGAAAACAAAACA-3' and 5'-
TATGTTTTGTTTTCAAGATTTAAGCC-3'. The linker sequence in pET-*fabI* was
25 confirmed by dideoxy sequencing. Only native FabI was used for compound evaluation. For overproduction of native FabI, plasmid pET-*fabI* was transformed into BL21(DE3) (Novagen) cells, to form strain BL21(DE3):pET-*fabI*.

Purification of *S. aureus* FabI

S. aureus FabI was expressed as soluble protein to 10% of total cell protein, 400g cells being recovered from 15L fermentation in tryptone phosphate medium. The cells were lysed and the sample centrifuged. The resulting supernatant was filtered and purified using three consecutive chromatography columns: ion-exchange (Source 15Q), dye-affinity (Blue sepharose), and size exclusion chromatography columns (Superose 12). After each column the FabI containing fractions were pooled, concentrated, and checked for purity and biological activity.

Cloning of *E. coli* FabI:

A PCR fragment of correct size for *E. coli* FabI was PCR amplified from *E. coli* chromosomal DNA, subcloned into the TOPO TA cloning vector, and verified by colony PCR + restriction endonuclease analysis. The presumptive *E. coli* FabI PCR fragment was subcloned into the expression vector pBluePet. The FabI clone was transformed into *E. coli* strain BL21(DE3). Small Scale expression studies show an over-expressed protein band of correct molecular weight (~28 Kda) for *E. coli* FabI clearly visible following Coomassie staining of SDS PAGE gels. DNA sequencing of the *E. coli* FabI expression constructs illustrated that no errors were apparent. N' terminal amino acid sequencing has confirmed the over-expressed protein band to be *E. coli* FabI.

Purification of *E. coli* FabI

E. coli FabI was expressed as soluble protein to 15% of total cell protein, 120g cells being recovered from 3L fermentation in shake flasks in modified terrific broth. The cells were lysed and the sample centrifuged. The resulting supernatant was filtered and purified using three consecutive chromatography columns: ion-exchange (Source 15Q), dye-affinity (blue sepharose), and size exclusion (superose 12). After each column the FabI containing fractions were pooled, concentrated and checked for purity and biological activity.

S. aureus FabI Enzyme Inhibition Assay (NADH):

Assays were carried out in half-area, 96-well microtitre plates. Compounds were evaluated in 50-uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-[2-acetamido]-2-iminodiacetic acid), 4 % glycerol, 0.25 mM crotonoyl CoA, 1 mM NADH, and an appropriate dilution of *S. aureus* FabI. Inhibitors were typically varied over the range of 0.01-10 uM. The consumption of NADH was monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities were estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at t = 0 min. IC₅₀'s were estimated from a fit of the initial velocities to a standard, 4-parameter model and are typically reported as the mean ± S.D. of duplicate determinations. Triclosan, a commercial antibacterial agent and inhibitor of FabI, is currently included in all assays as a positive control. Compounds of this invention have IC₅₀'s from about 5.0 micromolar to about 0.05 micromolar.

S. aureus FabI Enzyme Inhibition Assay (NADPH):

Assays were carried out in half-area, 96-well microtitre plates. Compounds were evaluated in 150-uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-[2-acetamido]-2-iminodiacetic acid), 4 % glycerol, 0.25 mM crotonoyl CoA, 50 uM NADPH, and an appropriate dilution of *S. aureus* FabI. Inhibitors were typically varied over the range of 0.01-10 uM. The consumption of NADPH was monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities were estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at t = 0 min. IC₅₀'s were estimated from a fit of the initial velocities to a standard, 4-parameter model and are typically reported as the mean ± S.D. of duplicate determinations. Triclosan, a commercial antibacterial agent and inhibitor of FabI, is currently included in all assays as a positive control.

E. coli FabI Enzyme Inhibition Assay:

Assays were carried out in half-area, 96-well microtitre plates. Compounds were evaluated in 150-uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-[2-acetamido]-2-iminodiacetic acid), 4 % glycerol, 0.25 mM crotonoyl CoA, 50 uM NADH, and an appropriate dilution of *E. coli* FabI. Inhibitors were typically varied over the range of 0.01-10 uM. The consumption of NADH was monitored for 20 minutes at 30 °C by

following the change in absorbance at 340 nm. Initial velocities were estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at $t = 0$ min. IC_{50} 's were estimated from a fit of the initial velocities to a standard, 4-parameter model and are typically reported as the mean \pm S.D. of duplicate determinations. Triclosan, a commercial antibacterial agent and inhibitor of FabI, is currently included in all assays as a positive control. Compounds of this invention have IC_{50} 's from about 100.0 micromolar to about 0.05 micromolar.

Preparation and purification of crotonoyl-ACP:

Reactions contained 5 mg/mL *E. coli* apo-ACP, 0.8 mM crotonoyl-CoA (Fluka), 10 mM $MgCl_2$, and 30 μ M *S. pneumoniae* ACP synthase in 50 mM NaHEPES, pH 7.5. The mixture was gently mixed on a magnetic stirrer at 23 °C for 2 hr, and the reaction was terminated by the addition of 15 mM EDTA. The reaction mixture was filtered through a 0.2 micron filter (Millipore) and applied to a MonoQ column (Pharmacia) equilibrated with 20 mM Tris-Cl, pH 7.5. The column was washed with buffer until all non-adherent material was removed (as observed by UV detection), and the crotonoyl-ACP was eluted with a linear gradient of 0 to 400 mM NaCl.

S. aureus FabI Enzyme Inhibition Assay using crotonoyl-ACP:

Assays are carried out in half-area, 96-well microtitre plates. Compounds are evaluated in 150 μ L assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-(2-acetamido)-2-iminodiacetic acid), 4 % glycerol, 25 μ M crotonoyl-ACP, 50 μ M NADPH, and an appropriate dilution of *S. aureus* Fab I (approximately 20 nM). Inhibitors are typically varied over the range of 0.01-10 μ M. The consumption of NADPH is monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities are estimated from a linear fit of the progress curves. IC_{50} 's are estimated from a fit of the initial velocities to a standard, 4-parameter model (Equation 1) and are typically reported as the mean \pm S.D. of duplicate determinations. Compounds of this invention in this assay have IC_{50} 's from about 100.0 micromolar to about 0.04 micromolar. The apparent K_i is calculated from Equation 2 assuming the inhibition is competitive with crotonoyl-ACP.

Equation 1: $v = \text{Range}/(1+[I]/IC_{50}) + \text{Background}$

Equation 2: $K_i(\text{app}) = IC_{50}/(1+[S]/K_s)$

FabK Enzyme Inhibition Assay

5 FabK catalyses the reduction of enoyl-ACPs with the concomitant oxidation of NADH. The reduction of crotonoyl-ACP to butyryl-ACP can be monitored by following the change in absorbance at 340 nm as NADH is oxidized.

Assays were carried out in Costar 3696 half-area plates in a final assay volume of 150 uL on a Spectramax platereader. The substrates (NADH and crotonoyl-ACP) were incubated with FabK enzyme in 100 mM N-[2-acetamido]-2 iminodiacetic acid (ADA), pH 10 6.5, 100 mM NH₄Cl, 4% glycerol at 30 °C and the reaction was monitored at 340 nm.

Using the above assay, compounds were tested for inhibition of FabK. 30 uL of inhibitor was added to a well of the plate. 30 uL of a 250 uM stock of NADH and 60 uL of a 67.5 uM stock of crotonoyl ACP were then added to the well. The plate was incubated at 30 °C for 5 min. The reaction was initiated by adding 30 uL of a 6.25 nM stock of enzyme 15 to the well (also pre-incubated at 30 °C). The reaction was then monitored at A340 nm for 30 min at 30 °C. Positive controls were reactions without compound. Negative controls were reactions without enzyme and without compound. Final concentrations in the assay mixture were 25 uM crotonoyl-ACP, 50 uM NADH, and 1.25 nM enzyme.

IC₅₀s were determined for compounds by carrying out the assay at 8 different 20 concentrations of compound (100 uM-0.75 uM) in duplicate. The IC₅₀ was calculated using Grafit software (v 4.09). The two Fab K inhibitors of this invention have IC₅₀'s of about 5 micromolar.

Antimicrobial Activity Assay:

25

Whole-cell antimicrobial activity was determined by broth microdilution using the National Committee for Clinical Laboratory Standards (NCCLS) recommended procedure, Document M7-A4, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically". The compound was tested in serial two-fold dilutions ranging from 0.06 to 30 64 mcg/mL. Test organisms were selected from the following laboratory strains: *Staphylococcus aureus* Oxford, *Staphylococcus aureus* WCUH29, *Streptococcus pneumoniae* ERY2, *Streptococcus pneumoniae* 1629, *Streptococcus pneumoniae* N 1387, *Enterococcus faecalis* I, *Enterococcus faecalis* 7, *Haemophilus influenzae* Q1, *Haemophilus influenzae* NEMC1, *Moraxella Catarrhalis* 1502, *Escherichia coli* 7623 35 *AcrABEFD+*, *Escherichia coli* 120 *AcrAB-*, *Escherichia coli* MG1655, *Escherichia coli* MG1658. The minimum inhibitory concentration (MIC) was determined as the lowest

concentration of compound that inhibited visible growth. A mirror reader was used to assist in determining the MIC endpoint.

One skilled in the art would consider any compound with a MIC of less than 256 $\mu\text{g/mL}$ to be a potential lead compound. Preferably, the compounds used in the antimicrobial assays of the present invention have a MIC value of less than 128 $\mu\text{g/mL}$.
5 Most preferably, said compounds have a MIC value of less than 64 $\mu\text{g/mL}$.

According to the instant invention, the preferred Fab I and Fab K enzyme inhibition assays use crotonoyl-ACP, rather than crotonoyl CoA, as a substrate. Thus, this invention comprises the preparation and purification of crotonoyl-ACP and the use of this purified
10 enzyme in Fab I and Fab K enzyme inhibition assays. Crotonoyl-ACP was synthesised using *S. pneumoniae* ACP synthase to catalyse the addition of a crotonoyl group from crotonoyl CoA to *E.coli* apo-acyl carrier protein (ACP). In a further aspect of this invention, it is contemplated that an apo-acyl carrier protein from any bacterial species, such as from *Escherichia coli*, *Staphylococcus* and *Streptococcus*, can be used in the
15 preparation of crotonoyl-ACP. This synthesis was carried out in the presence of magnesium chloride in NaHEPES, pH 7.5. The reaction was complete in 2 hours at a reaction temperature of about 20-30°C, preferably at 23°C.

The purified crotonoyl-ACP prepared above is then used in the Fab I and Fab K assays to determine the inhibitors of the instant invention. Assays may be carried out, for
20 example, in Costar 3696 half-area plates, preferably at a final assay volume of 150 μL on a Spectramax platereader. Preferred substrates used in the methods of the invention are NADH, NADPH, an NADH analogue and crotonoyl-ACP. Further provided are preferred methods comprising the step of incubating substrates with Fab I or Fab K in 100 mM N-[2-acetamido]-2 iminodiacetic acid (ADA), pH 6.5. This reaction may be monitored at 340
25 nm, among other wavelengths.

The examples which follow are intended in no way to limit the scope of this invention, but are provided to illustrate how to make and use the compounds of this invention. Many other embodiments will be readily apparent to those skilled in the art.

EXAMPLES

General

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at either 300 or 360 MHz, and chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS). Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. CDCl_3 is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Mass spectra were obtained using electrospray (ES) ionization techniques. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius. Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Flash chromatography was carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical HPLC was performed on Beckman chromatography systems. Preparative HPLC was performed using Gilson chromatography systems. ODS refers to an octadecylsilyl derivatized silica gel chromatographic support. YMC ODS-AQ® is an ODS chromatographic support and is a registered trademark of YMC Co. Ltd., Kyoto, Japan. PRP-1® is a polymeric (styrene-divinylbenzene) chromatographic support, and is a registered trademark of Hamilton Co., Reno, Nevada. Celite® is a filter aid composed of acid-washed diatomaceous silica, and is a registered trademark of Manville Corp., Denver, Colorado.

Preparation 1

Preparation of 1-methyl-2-(methylaminomethyl)-1*H*-indole

5 a) Ethyl 1-methyl-1*H*-indole-2-carboxylate

NaH (60% dispersion in mineral oil, 8.02 g, 200.49 mmole) was washed with hexanes, then was suspended in dry DMF (530 mL). Solid ethyl indole-2-carboxylate (25.29 g, 133.66 mmole) was added portionwise over 5 - 10 min, allowing gas evolution to subside between additions. When the addition was complete, the yellow mixture was
10 stirred for 15 min, then methyl iodide (42 mL, 668.3 mmole) was added all at once. The reaction was exothermic, and the internal temperature rose to 40 - 45°C. After 1 hr, the reaction was quenched with 10% NH₄Cl (100 mL) and concentrated on the rotavap (high vacuum). The residue was partitioned between Et₂O (500 mL) and H₂O (100 mL), and the layers were separated. The Et₂O layer was washed with H₂O (100 mL), dried (MgSO₄),
15 and concentrated to leave the title compound (27.10 g, quantitative) as a light yellow solid. This was used without further purification: TLC (10% EtOAc/hexanes) R_f = 0.39.

b) N,1-Dimethyl-1*H*-indole-2-carboxamide

A suspension of ethyl 1-methyl-1*H*-indole-2-carboxylate (27.10 g, 133.34 mmole)
20 in 40% aqueous CH₃NH₂ (300 mL) and MeOH (30 mL) was stirred at RT. A solid tended to gradually creep up the walls of the flask, and was washed down periodically with MeOH. The flask was tightly stoppered to keep the material inside the flask. As the reaction proceeded, the solid dissolved, but eventually the product began to precipitate. The reaction was stirred at RT for 5 days, then was concentrated to remove approximately 200
25 mL of the solvent. The remaining residue was diluted with H₂O (300 mL), and the solid was collected by suction filtration and washed with H₂O. Drying at 50 - 60°C in high vacuum left the title compound (23.45 g, 93%) as a faintly yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 7.63 (d, J = 8.0 Hz, 1 H), 7.27 - 7.43 (m, 2 H), 7.10 - 7.20 (m, 1 H), 6.80 (s, 1 H), 6.10 - 6.30 (m, 1 H), 4.06 (s, 3 H), 3.01 (d, J = 4.9 Hz, 3 H).

30

c) 1-Methyl-2-(methylaminomethyl)-1*H*-indole

A 3-liter 3-necked roundbottom flask equipped with overhead stirring was charged with N,1-dimethyl-1*H*-indole-2-carboxamide (23.45 g, 124.58 mmole) and anhydrous THF (170 mL). The solution was stirred while a solution of LiAlH₄ in THF (1.0 M, 250 mL,
35 250 mmole) was added via syringe. Gas was evolved during the addition of the first 50 mL of LiAlH₄ solution. When the addition was complete, the resulting light yellow solution

was heated at gentle reflux. After 23 hr, the reaction was cooled in ice and quenched by the sequential dropwise addition of H₂O (9.5 mL), 15% NaOH (9.5 mL), and H₂O (28.5 mL). The mixture was stirred for 15 min, then was filtered through celite®, and the filter pad was washed thoroughly with THF. The filtrate was concentrated and the residue was flash chromatographed on silica gel (10% MeOH/CHCl₃ containing 0.5% conc. NH₄OH). The title compound (20.17 g, 93%) was obtained as a light yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 7.56 (d, J = 7.8 Hz, 1 H), 7.02 - 7.35 (m, 3 H), 6.38 (s, 1 H), 3.88 (s, 2 H), 3.75 (s, 3 H), 2.49 (s, 3 H).

Preparation 2

Preparation of (E)-3-(6-aminopyridin-3-yl)acrylic acid (Method A)

a) Benzyl (E)-3-(6-aminopyridin-3-yl)acrylate

A solution of 2-amino-5-bromopyridine (2.25 g, 13.0 mmole), benzyl acrylate (3.2 g, 19.7 mmole), Pd(OAc)₂ (0.31 g, 1.4 mmole), tri-*ortho*-tolylphosphine (0.73 g, 2.4 mmole), and diisopropylethylamine (3.5 mL, 20.0 mmole) in propionitrile (50 mL) was heated at reflux overnight. The dark mixture was filtered through celite®, and the filtrate was concentrated. Flash chromatography on silica gel (3% MeOH/CH₂Cl₂) gave the title compound (1.3 g, 39%): MS (ES) *m/e* 255 (M + H)⁺.

b) (E)-3-(6-Aminopyridin-3-yl)acrylic acid

A solution of benzyl (E)-3-(6-aminopyridin-3-yl)acrylate (1.3 g, 5.1 mmole) and 1.0 N NaOH (10 mL, 10 mmole) in MeOH was heated at reflux overnight. The solution was concentrated in vacuo, and the residue was dissolved in H₂O. The pH was adjusted to 6 with dilute HCl, and the solid precipitate was collected by suction filtration and dried to give the title compound (0.6 g, 72%) as a white solid: MS (ES) *m/e* 165 (M + H)⁺.

Preparation 3

Preparation of (E)-3-(6-aminopyridin-3-yl)acrylic acid (Method B)

a) (E)-3-(6-Aminopyridin-3-yl)acrylic acid

Acrylic acid (23 mL, 0.33 mole) was added carefully to a solution of 2-amino-5-bromopyridine (25.92 g, 0.15 mole) and Na₂CO₃ (55.64 g, 0.53 mole) in H₂O (600 mL). PdCl₂ (0.53 g, 0.003 mole) was then added, and the mixture was heated at reflux. After 24

hr, the reaction was cooled to RT and filtered, and the filtrate was adjusted to pH 6 with aqueous HCl. Additional H₂O (0.5 L) was added to improve mixing, and the mixture was stirred for 1 hr. The pH was readjusted to 6, then the solid was collected by suction filtration. The filter pad was washed sequentially with H₂O (2 x 0.5 L), cold absolute EtOH (100 mL), and Et₂O (2 x 250 mL). Drying in high vacuum at elevated temperature gave the title compound (15.38 g, 62%) as a tan solid: ¹H NMR (300 MHz, DMSO-d₆) δ 8.11 (d, J = 2.0 Hz, 1 H), 7.75 (dd, J = 8.7, 2.0 Hz, 1 H), 7.43 (d, J = 15.8 Hz, 1 H), 6.53 (s, 2 H), 6.45 (d, J = 8.7 Hz, 1 H), 6.22 (d, J = 15.8 Hz, 1 H); MS (ES) *m/e* 165 (M + H)⁺.

10

Preparation 4

Preparation of 1-methyl-3-(methylaminomethyl)-1*H*-indazole

a) Methyl (1-methyl-1*H*-indazole)carboxylate

15 Indazole-3-carboxylic acid (5.0 g, 30 mmole), K₂CO₃ (12.4 g, 90 mmole), and MeI (9.3 mL, 150 mmole) were combined in dry DMF (100 mL) and heated to 50 °C. After 18 hr the mixture was cooled to RT and concentrated *in vacuo*. The residue was taken up in EtOAc and filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (25% EtOAc/hexanes) to give the title compound (3.88 g, 68%) as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 8.24 (m, 1 H), 7.47 (m, 2 H), 7.34 (m, 1 H), 4.19 (s, 3 H), 4.05 (s, 3 H).

b) N,1-Dimethyl-1*H*-indazole-3-carboxamide

25 A suspension of methyl (1-methyl-1*H*-indazole)carboxylate (3.88 g, 20.4 mmole) in 40% aqueous CH₃NH₂ (100 mL) and MeOH (5 mL) was stirred at RT for 4 hr. During that time the suspension became a solution. The mixture was concentrated to approximately 1/3 by volume at which time the product precipitated as a pale yellow solid. The solid was collected by filtration, washed with H₂O, and dried *in vacuo* to give the title compound (3.42 g, 89%) which was sufficiently pure for use in the next step: ¹H NMR (300 MHz, CDCl₃) δ 8.24 (m, 1 H), 7.47 (m, 2 H), 7.34 (m, 1 H), 6.95 (bs, 1 H), 4.19 (s, 3 H), 3.05 (d, J = 12.0 Hz, 3 H).

30

c) 1-Methyl-3-(methylaminomethyl)-1*H*-indazole

35 To a solution of N,1-dimethyl-1*H*-indazole-3-carboxamide (3.42 g, 18 mmole) in dry THF (90 mL) was added a solution of LiAlH₄ in THF (1.0 M, 36 mL, 36 mmole) slowly at RT. After 2 hr the mixture was heated to a gentle reflux. After 4 hr the mixture

was cooled to RT and quenched by dropwise addition of 2.0 M NaOH until a white solid had formed. The mixture was dried (MgSO₄), filtered, and concentrated under reduced pressure to give the title compound (3.28 g, 100%) as an oil which was sufficiently pure for use in the next step: MS (ES) *m/e* 176 (M + H)⁺.

5

Preparation 5

Preparation of (E)-3-(3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl)acrylic acid

10 a) 3,4-Dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine

To a suspension of 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (2.0 g, 13.3 mmole) in dry THF (40 mL) was added a solution of LiAlH₄ in THF (1.0 M, 26.6 mL, 26.6 mmole) slowly at 0°C. After 1 hr the mixture was quenched with 2.0 M NaOH until a solid formed. The mixture was dried (MgSO₄), filtered, and concentrated under reduced pressure to give
15 the title compound (1.44 g, 79%) as a white solid which was sufficiently pure for use in the next step: MS (ES) *m/e* 137 (M + H)⁺.

b) 4-(*tert*-Butoxycarbonyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine

To a solution of 3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine (1.44 g, 10.6 mmole)
20 and di-*tert*-butyl dicarbonate (2.78 g, 12.7 mmole) in dry THF (50 mL) was added a solution of LiHMDS in THF (1.0 M, 12.7 mL, 12.7 mmole) dropwise at 0°C. After 30 min the mixture was quenched with saturated NH₄Cl and extracted with EtOAc (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash chromatography on silica gel (40% EtOAc/hexanes) gave the title compound (2.0 g, 80%)
25 as a clear oil: MS (ES) *m/e* 237 (M + H)⁺.

c) 4-(*tert*-Butoxycarbonyl)-7-bromo-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine

To a solution of 4-(*tert*-butoxycarbonyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine (2.0 g, 8.46 mmole) in MeOH (40 mL) was added Br₂ (0.53 mL, 10.2 mmole) dropwise at
30 0°C. After 1 hr the mixture was concentrated. The residue was taken up in 1:1 Et₂O/hexanes and filtered. The filtrate was concentrated under reduced pressure to give the title compound (1.27 g, 48%) as an oil which solidified under vacuum: ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1 H), 7.33 (s, 1 H), 4.25 (m, 2 H), 3.92 (m, 2 H), 1.54 (s, 9 H).

d) (E)-3-[4-(*tert*-Butoxycarbonyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl]acrylic acid

A solution of 4-(*tert*-butoxycarbonyl)-7-bromo-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine (1.27 g, 4.03 mmole), benzyl acrylate (785 mg, 4.84 mmole), Pd(OAc)₂ (45 mg, 0.20 mmole), P(*o*-tolyl)₃ (122 mg, 0.4 mmole), and (*i*-Pr)₂NEt (1.76 mL, 10.1 mmole) in propionitrile (20 mL) was degassed (3 x N₂/vacuum) then heated to reflux. After 18 hr the mixture was cooled to RT and concentrated. Flash chromatography on silica gel (25% EtOAc/hexanes) gave the title compound (1.17 g, 73%) as a yellow oil: MS (ES) *m/e* 397 (M + H)⁺.

e) (E)-3-(3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)acrylic acid

(E)-3-[4-(*tert*-Butoxycarbonyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl]acrylic acid (1.17 g, 2.95 mmole) was dissolved in 4 N HCl in dioxane (15 mL). After 72 hr the mixture was concentrated. The residue was taken up in 1:1 MeOH/H₂O (20 mL). 1.0 N LiOH (15 mL, 15 mmole) was added and the mixture was heated to reflux. After 18 hr the mixture was cooled to RT and concentrated to approximately 1/3 volume. The mixture was adjusted to pH 6 using 10% HCl. The solid was collected by filtration, washed with H₂O and dried *in vacuo* to give the title compound (315 mg, 52% over 2 steps): MS (ES) *m/e* 207 (M + H)⁺.

Preparation 6

Preparation of (E)-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid

a) 1,2,3,4-Tetrahydro-1,8-naphthyridine

1,8-Naphthyridine (1.0 g, 7.68 mmole) was hydrogenated (50 psi) with 10% Pd/C (100 mg) in absolute ethanol (40 mL) for 18 hr. The mixture was filtered through a pad of Celite® and the filtrate was concentrated to give the title compound (1.04 g) which was sufficiently pure for use in the next step: MS (ES) *m/e* 135 (M + H)⁺.

b) 1-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro-1,8-naphthyridine

To a solution of 1,2,3,4-tetrahydro-1,8-naphthyridine (1.04 g, 7.68 mmole) and di-*tert*-butyl dicarbonate (2.01 g, 9.22 mmole) in dry THF (40 mL) was added a solution of LiHMDS in THF (1.0 M, 9.22 mL, 9.22 mmole) dropwise at 0°C. After 30 min the mixture was quenched with saturated NH₄Cl and extracted with EtOAc (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash chromatography on

silica gel (40% EtOAc/hexanes) gave the title compound (1.37 g, 76% over 2 steps) as an orange oil which solidified under vacuum: ^1H NMR (400 MHz, CDCl_3) δ 8.33 (m, 1 H), 7.37 (m, 1 H), 6.94 (m, 1 H), 3.77 (m, 2 H), 2.75 (t, $J = 6.5$ Hz, 2 H), 1.93 (m, 2 H), 1.54 (s, 9 H).

5

c) 1-(*tert*-Butoxycarbonyl)-6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridine

To a solution of 1-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydro-1,8-naphthyridine (1.37 g, 5.85 mmole) in CH_2Cl_2 (30 mL) was added glacial HOAc (3.4 mL, 58.5 mmole) and NBS (1.09 g, 6.14 mmole). After 72 hr the mixture was washed with 2.0 M NaOH, H_2O , and brine. The mixture was dried (MgSO_4), filtered, and concentrated under reduced pressure to give the title compound (1.79 g, 98%) which was sufficiently pure for use in the next step: ^1H NMR (400 MHz, CDCl_3) δ 8.35 (s, 1 H), 7.51 (s, 1 H), 3.77 (m, 2 H), 2.75 (t, $J = 6.5$ Hz, 2 H), 1.93 (m, 2 H), 1.54 (s, 9 H).

10

15 d) Benzyl (E)-3-[8-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]acrylate

A solution of 1-(*tert*-butoxycarbonyl)-6-bromo-1,2,3,4-tetrahydro-1,8-naphthyridine (1.79 g, 5.70 mmole), benzyl acrylate (1.11 g, 6.84 mmole), $\text{Pd}(\text{OAc})_2$ (65 mg, 0.29 mmole), $\text{P}(\text{o-tolyl})_3$ (173 mg, 0.57 mmole), and (*i*-Pr) $_2\text{NEt}$ (2.5 mL, 14.25 mmole) in propionitrile (30 mL) was degassed (3 x N_2 /vacuum) then heated to reflux. After 18 hr the mixture was cooled to RT and concentrated. Flash chromatography on silica gel (25% EtOAc/hexanes) gave the title compound (1.21 g, 54%) as a yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 8.44 (s, 1 H), 7.65 (d, $J = 16.0$ Hz, 1 H), 7.53 (s, 1 H), 7.40 (m, 5 H), 6.43 (d, $J = 16.0$ Hz, 1 H), 5.25 (s, 2 H), 3.77 (m, 2 H), 2.75 (t, $J = 6.5$ Hz, 2 H), 1.93 (m, 2 H), 1.54 (s, 9 H)

20

25 e) (E)-3-(5,6,7,8-Tetrahydro-1,8-naphthyridin-3-yl)acrylic acid

Benzyl (E)-3-[8-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]acrylate (1.21 g, 3.07 mmole) was dissolved in 4 N HCl in dioxane (15 mL). After 18 hr the mixture was concentrated. The residue was taken up in 1:1 MeOH/ H_2O (15 mL). 1.0 N LiOH (15 mL, 15 mmole) was added and the mixture heated to reflux. After 18 hr the mixture was cooled to RT and concentrated to approximately 1/3 volume. The mixture was adjusted to pH 6 using 10% HCl. The solid was collected by filtration, washed with H_2O , and dried *in vacuo* to give the title compound (180 mg, 29% over 2 steps): MS (ES) m/e 205 ($\text{M} + \text{H}$) $^+$.

30

35

Preparation 7Preparation of 2-(methylaminomethyl)thieno[2,3-*b*]thiophene

5 a) 3-(1,3-Dioxolan-2-yl)thiophene

To a solution of thiophene-3-carboxaldehyde (5.0 g, 44.58 mmole) in benzene (200 mL) was added ethylene glycol (25 mL, 445.8 mmole) and *p*-toluenesulfonic acid hydrate (848 mg, 4.458 mmole). The mixture was heated to reflux under a Dean-Stark trap. After 18 hr the mixture was cooled to RT, washed with saturated NaHCO₃ then with H₂O, dried
10 (MgSO₄), and concentrated under reduced pressure to give the title compound (6.32 g, 91%) as a light amber oil: ¹H NMR (400 MHz, CDCl₃) δ 7.42 (s, 1 H), 7.32 (m, 1 H), 7.16 (m, 1 H), 5.91 (s, 1 H), 4.12-3.99 (m, 4 H).

15 b) 2-(Carboethoxymethylthio)-3-(1,3-dioxolan-2-yl)thiophene

To a solution of 3-(1,3-dioxolan-2-yl)thiophene (6.32 g, 40.46 mmole) in dry THF (200 mL) was added a solution of *n*-BuLi in hexanes (1.7 M, 28.8 mL, 49 mmole) slowly at -78°C. After 30 min sulfur (1.57 g, 49 mmole) was added all at once. After 30 min ethyl bromoacetate (7.4 mL, 66.87 mmole) was added slowly, and after another 30 min the mixture was warmed to RT. After 2 hr at RT the mixture was concentrated under reduced
20 pressure. The residue was taken up in Et₂O, washed with H₂O (3x), dried (MgSO₄), and concentrated to give the title compound as an oil which was sufficiently pure for use in the next step.

25 c) 2-(Carboethoxymethylthio)-3-formylthiophene

To a solution of 2-(carboethoxymethylthio)-3-(1,3-dioxolan-2-yl)thiophene (from step b) in acetone (200 mL) was added *p*-toluenesulfonic acid (761 mg, 4.0 mmole) at RT. After 18 hr the mixture was concentrated. The residue was taken up in Et₂O, washed with saturated NaHCO₃, H₂O (2x), dried (MgSO₄), and concentrated under reduced pressure to give the title compound as an oil which was sufficiently pure for use in the next step.

30

d) Ethyl thieno[2,3-*b*]thiophene-2-carboxylate

To a solution of 2-(carboethoxymethylthio)-3-formylthiophene (from step c) in MeOH (200 mL) was added DBU (0.6 mL, 4.0 mmole) at 0°C. After 1 hr the mixture was warmed to RT and concentrated. The residue was taken up in EtOAc, washed with 10%
35 HCl, H₂O (3x), dried (MgSO₄), and concentrated. Flash chromatography on silica gel (50% toluene/hexanes) gave the title compound (3.84 g, 45% over 4 steps) as an off-white

solid: ^1H NMR (400 MHz, CDCl_3) δ 7.95 (s, 1 H), 7.40 (d, J = 5.2 Hz, 1 H), 7.26 (d, J = 5.2 Hz, 1 H), methyl ester 3.92 (s, 3 H), ethyl ester 4.38 (q, J = 7.1 Hz, 2 H) and 1.41 (t, J = 2.4 Hz, 3 H).

5 e) N-Methyl-2-(thieno[2,3-*b*]thiophene)carboxamide

A suspension of ethyl thieno[2,3-*b*]thiophene-2-carboxylate (3.84 g, 18.1 mmole) in 40% aqueous CH_3NH_2 (100 mL) and MeOH (10 mL) was stirred at RT for 18 hr. During that time the suspension became a solution. The mixture was concentrated to approximately 1/3 volume at which time the product precipitated. The solid was collected
10 by filtration, washed with H_2O , and dried *in vacuo* to give the title compound (3.01 g, 85%): ^1H NMR (400 MHz, $\text{d}^6\text{-DMSO}$) δ 8.60 (bs, 1 H), 7.92 (s, 1 H), 7.67 (d, J = 5.2 Hz, 1 H), 7.38 (d, J = 5.2 Hz, 1 H), 2.78 (d, J = 4.6 Hz, 3 H).

f) 2-(Methylaminomethyl)thieno[2,3-*b*]thiophene

15 To a solution of N-methyl-2-(thieno[2,3-*b*]thiophene)carboxamide (3.01 g, 15.26 mmole) in dry THF (75 mL) was added a solution of LiAlH_4 in THF (1.0 M, 30 mL, 30 mmole) slowly at RT. After gas evolution had ceased the mixture was heated to a gentle reflux. After 18 hr the mixture was cooled to RT and quenched by dropwise addition of 2.0 M NaOH until a white solid had formed. The mixture was dried over MgSO_4 , filtered, and
20 concentrated under reduced pressure to give the title compound (2.18 g, 78%) as a brown oil: ^1H NMR (400 MHz, CDCl_3) δ 7.30 (d, J = 5.2 Hz, 1 H), 7.15 (d, J = 5.2 Hz, 1 H), 7.04 (s, 1 H), 4.00 (s, 2 H), 2.49 (s, 3 H).

Preparation 8

25

Preparation of 2-(methylaminomethyl)thieno[3,2-*b*]thiophene

a) N-Methyl-2-(thieno[3,2-*b*]thiophene)carboxamide

EDC (624 mg, 3.26 mmole) was added to a solution thieno[3,2-*b*]thiophene-2-
30 carboxylic acid (500 mg, 2.71 mmole), CH_3NH_2 (2.0 M in THF, 2.7 mL, 5.42 mmole), HOBT \cdot H_2O (440 mg, 3.26 mmole), and Et_3N (0.95 mL, 6.78 mmole) in dry DMF (14 mL) at RT. After 18 hr the mixture was diluted with H_2O and extracted with EtOAc (3x). The combined organic layers were dried (MgSO_4) and concentrated to give the title compound (415 mg, 78%) which was sufficiently pure for use in the next step: ^1H NMR (400 MHz,
35 CDCl_3) δ 7.70 (s, 1 H), 7.52 (d, J = 5.3 Hz, 1 H), 7.27 (d, J = 5.3 Hz, 1 H), 3.02 (d, J = 4.9 Hz, 3 H).

b) 2-(Methylaminomethyl)thieno[3,2-*b*]thiophene

To a solution of N-methyl-2-(thieno[3,2-*b*]thiophene)carboxamide (415 mg, 2.1 mmole) in dry THF (10 mL) was added a solution of LiAlH₄ in THF (1.0 M, 4.2 mL, 4.2 mmole) slowly at RT. After gas evolution had ceased the mixture was heated to a gentle reflux. After 18 hr the mixture was cooled to RT and quenched by dropwise addition of 2.0 M NaOH until a white solid had formed. The mixture was dried (MgSO₄), filtered, and concentrated to give the title compound (361 mg, 94%) as a brown oil: ¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, J = 5.2 Hz, 1 H), 7.21 (d, J = 5.2 Hz, 1 H), 7.11 (s, 1 H), 4.01 (s, 2 H), 2.50 (s, 3 H).

Preparation 9Preparation of (E)-3-(3*H*-imidazo[4,5-*b*]pyridin-6-yl)acrylic acid

15

a) 5-Bromo-2,3-diaminopyridine

To a suspension of 2-amino-5-bromo-3-nitropyridine (2.0 g, 9.17 mmole) in absolute EtOH (50 mL) was added SnCl₂ hydrate (9.3 g, 41.3 mmole), then the mixture was heated to reflux. After 3 hr the mixture was cooled to RT and concentrated. The residue was taken up in 2.0 M NaOH and extracted with EtOAc (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated to give the title compound (1.69 g, 98%) which was sufficiently pure for use in the next step: MS (ES) *m/e* 188/190 (M + H)⁺.

25 b) 6-Bromo-3*H*-imidazo[4,5-*b*]pyridine

5-Bromo-2,3-diaminopyridine (1.69 g, 8.99 mmole) was taken up in 96% formic acid (50 mL) and heated to reflux. After 18 hr the mixture was cooled to RT and concentrated. The residue was taken up in H₂O and the pH was adjusted to 7 with 2.0 M NaOH. The title compound (1.54 g, 87%) was collected as a solid by filtration, washed with H₂O, and dried *in vacuo*: MS (ES) *m/e* 198/200 (M + H)⁺.

30

c) 6-Bromo-4-trityl-3*H*-imidazo[4,5-*b*]pyridine

To a suspension of 6-bromo-3*H*-imidazo[4,5-*b*]pyridine (1.2 g, 6.06 mmole) in CH₂Cl₂ (30 mL) was added Et₃N (1.3 mL, 9.09 mmole) then trityl chloride (2.03 g, 7.27 mmole) at RT. After 72 hr the mixture was washed with H₂O (2x) and brine, then was

35

dried (MgSO₄), filtered, and concentrated under reduced pressure to afford the title compound. This was used directly in the next step.

d) Benzyl (E)-3-(4-trityl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)acrylate

5 A solution of 6-bromo-4-trityl-3*H*-imidazo[4,5-*b*]pyridine (from step a) (6.06 mmole), benzyl acrylate (1.18 g, 7.27 mmole), Pd(OAc)₂ (67 mg, 0.30 mmole), P(*o*-tolyl)₃ (183 mg, 0.6 mmole), and (*i*-Pr)₂NEt (2.64 mL, 15.15 mmole) in propionitrile (30 mL) was degassed (3 x N₂/vacuum) then heated to reflux. After 4 hr the mixture was cooled to RT and concentrated. Flash chromatography on silica gel (30% EtOAc/hexanes) gave the title
10 compound (1.75 g, 55% over 2 steps) as an off-white foam: ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J* = 2.0 Hz, 1 H), 8.19 (d, *J* = 2.0 Hz, 1 H), 8.06 (s, 1 H), 7.77 (d, *J* = 16.0 Hz, 1 H), 7.42-7.11 (m, 20 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 5.25 (s, 2 H).

d) (E)-3-(3*H*-Imidazo[4,5-*b*]pyridin-6-yl)acrylic acid

15 Benzyl (E)-3-(4-trityl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)acrylate (1.75 g, 3.35 mmole)
was dissolved in 4 N HCl in dioxane (20 mL). After 1 hr the mixture was concentrated.
The residue was taken up in 1:1 MeOH/H₂O (15 mL). 2.0 N NaOH (15 mL, 15 mmole)
was added and the mixture was heated to reflux. After 18 hr the mixture was cooled to RT
and concentrated to approximately 1/3 volume. The mixture was adjusted to pH 4 using
20 10% HCl. The solid was collected by filtration, washed with H₂O, and dried *in vacuo* to
give the title compound (329 mg, 52% over 2 steps) as a white solid: ¹H NMR (400 MHz,
d⁶-DMSO) δ 9.10 (s, 1 H), 8.94 (s, 1 H), 8.84 (s, 1 H), 8.20 (d, J = 16.0 Hz, 1 H), 7.10 (d, J
= 16.0 Hz, 1 H).

25 Preparation 10

Preparation of 6-methyl-5-(methylaminomethyl)-6*H*-thieno[2,3-*b*]pyrrole

a) Ethyl (Z)-2-azido-3-(thiophen-3-yl)acrylate

To a solution of thiophene-3-carboxaldehyde (500 mg, 4.46 mmole) and ethyl 2-azido acetate (863 mg, 6.69 mmole) in absolute EtOH (20 mL) was added NaOEt (21%, 2.2 mL, 6.69 mmole) at 0°C. After 1 hr the mixture was quenched with saturated NH₄Cl and extracted with Et₂O (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash chromatography on silica gel (50% CHCl₃/hexanes) gave the title compound (208 mg, 21%) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.87 (m, 1

H), 7.49 (m, 1 H), 7.31 (m, 1 H), 6.96 (s, 1 H), 4.36 (q, $J = 7.1$ Hz, 2 H), 1.39 (t, $J = 7.1$ Hz, 3 H).

b) Ethyl 6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate

5 A solution of ethyl (Z)-2-azido-3-(thiophen-3-yl)acrylate (208 mg, 0.93 mmole) in xylenes (5 mL) was heated to reflux. After 30 min the mixture was cooled to RT and concentrated to give the title compound (175 mg, 96%) which was sufficiently pure for use in the next step: ^1H NMR (400 MHz, CDCl_3) δ 9.26 (bs, 1 H), 7.10 (m, 1 H), 7.00 (m, 1 H), 6.91 (m, 1 H), 4.36 (q, $J = 7.1$ Hz, 2 H), 1.39 (t, $J = 7.1$ Hz, 3 H).

10

c) N,6-Dimethyl-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

To a solution of ethyl 6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (175 mg, 0.9 mmole, see *J. Het. Chem.* **1984**, 21, 215-217) and MeI (0.08 mL, 1.35 mmole) in dry DMF (5 mL) was added NaH (60% dispersion in mineral oil, 43 mg, 1.08 mmole) at 0°C. After 2 hr the mixture was quenched with saturated NH_4Cl and extracted with EtOAc (3x). The combined organic layers were dried (MgSO_4), filtered, and concentrated to an oil.

15 A solution of the above oil in 40% aqueous CH_3NH_2 (20 mL) and MeOH (1 mL) was stirred at RT for 18 hr. The mixture was concentrated to approximately 1/3 by volume at which time the product precipitated. The solid was collected by filtration, washed with H_2O , and dried *in vacuo* to give the title compound (134 mg, 74% over 2 steps): MS (ES) m/e 195 ($\text{M} + \text{H}$) $^+$.

20

d) 6-Methyl-5-(methylaminomethyl)-6*H*-thieno[2,3-*b*]pyrrole

To a solution of N,6-dimethyl-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (134 mg, 0.69 mmole) in dry THF (5 mL) was added a solution of LiAlH_4 in THF (1.0 M, 1.38 mL, 1.38 mmole) slowly at RT. After gas evolution had ceased the mixture was heated to a gentle reflux. After 2 hr the mixture was cooled to RT and quenched by dropwise addition of 2M NaOH until a white solid had formed. The mixture was dried (MgSO_4), filtered, and concentrated to give the title compound as a brown oil (142 mg, 100%) which was sufficiently pure for use in the next step: ^1H NMR (400 MHz, CDCl_3) δ 6.95 (d, $J = 5.2$ Hz, 1 H), 6.78 (d, $J = 5.2$ Hz, 1 H), 6.27 (s, 1 H), 3.78 (s, 2 H), 3.72 (s, 3 H), 2.47 (s, 3 H).

30

Preparation 11Preparation of (E)-3-(2-aminopyrimidin-5-yl)acrylic acid

5 a) Benzyl (E)-3-(2-aminopyrimidin-5-yl)acrylate

According to the procedure of Preparation 2 (a), except substituting 5-bromo-2-aminopyrimidine (1.95 g, 11.2 mmole) for 2-amino-5-bromopyridine, the title compound (2.25 g, 79%) was prepared as a light orange solid: MS (ES) *m/e* 256 (M + H)⁺.

10 b) (E)-3-(2-Aminopyrimidin-5-yl)acrylic acid

According to the procedure of Preparation 2 (b), except substituting benzyl (E)-3-(2-aminopyrimidin-5-yl)acrylate (2.93 g, 11.5 mmole) for benzyl (E)-3-(6-aminopyridin-3-yl)acrylate, the title compound (1.71 g, 90%) was prepared as an off-white solid: MS (ES) *m/e* 166 (M + H)⁺.

15

Preparation 12Preparation of (E)-3-(6-aminopyridin-3-yl)-2-methylacrylic acid

20 a) Methyl (E)-3-(6-aminopyridin-3-yl)-2-methylacrylate

According to the procedure of Preparation 2 (a), except substituting methyl crotonate (4.33 g, 43.3 mmole) for benzyl acrylate, the title compound (1.0 g, 18%) was prepared as an off-white solid: MS (ES) *m/e* 193 (M + H)⁺.

25 b) (E)-3-(6-Aminopyridin-3-yl)-2-methylacrylic acid

According to the procedure of Preparation 2 (b), except substituting methyl (E)-3-(6-aminopyridin-3-yl)-2-methylacrylate (1.0 g, 5.2 mmole) for benzyl (E)-3-(6-aminopyridin-3-yl)acrylate, the title compound (0.83 g, 90%) was prepared as an off-white solid: MS (ES) *m/e* 179 (M + H)⁺.

30

Preparation 13Preparation of (E)-3-(6-amino-2-methylpyridin-3-yl)acrylic acid

- 5 a) Benzyl (E)-3-(6-amino-2-methylpyridin-3-yl)acrylate

According to the procedure of Preparation 2 (a), except substituting 2-amino-5-bromo-6-methylpyridine (5.00 g, 26.7 mmole) for 2-amino-5-bromopyridine, the title compound (5.58 g, 78%) was prepared as an off-white solid: MS (ES) *m/e* 269 (M + H)⁺.

- 10 b) (E)-3-(6-Amino-2-methylpyridin-3-yl)acrylic acid

According to the procedure of Preparation 2 (b), except substituting benzyl (E)-3-(6-amino-2-methylpyridin-3-yl)acrylate (2.20 g, 8.2 mmole) for benzyl (E)-3-(6-aminopyridin-3-yl)acrylate, the title compound (1.31 g, 90%) was prepared as an off-white solid: MS (ES) *m/e* 179 (M + H)⁺.

15

Preparation 14Preparation of (E)-3-(6-amino-5-methylpyridin-3-yl)acrylic acid

- 20 a) Benzyl (E)-3-(6-amino-5-methylpyridin-3-yl)acrylate

According to the procedure of Preparation 2 (a), except substituting 2-amino-5-bromo-3-methylpyridine (5.00 g, 26.7 mmole) for 2-amino-5-bromopyridine, the title compound (6.37 g, 89%) was prepared as an off-white solid: MS (ES) *m/e* 269 (M + H)⁺.

- 25 b) (E)-3-(6-Amino-5-methylpyridin-3-yl)acrylic acid

According to the procedure of Preparation 2 (b), except substituting benzyl (E)-3-(6-amino-5-methylpyridin-3-yl)acrylate (5.00 g, 18.6 mmole) for benzyl (E)-3-(6-aminopyridin-3-yl)acrylate, the title compound (2.98 g, 90%) was prepared as an off-white solid: MS (ES) *m/e* 179 (M + H)⁺.

30

Preparation 15Preparation of (E)-3-[6-amino-5-(hydroxymethyl)pyridin-3-yl]acrylic acid

5 a) 2-Amino-3-(hydroxymethyl)pyridine

To a solution of 2-aminonicotinic acid (20.5 g, 148.1 mmole) in THF was added lithium aluminum hydride (300 mL, 1.0 M in THF) over 30 minutes. The reaction solution was heated to reflux for 18 hrs and then was cooled to room temperature. The reaction was quenched by the sequential dropwise addition of H₂O (11.5 mL), 15% NaOH (11.5 mL),
10 and H₂O (34.5 mL). The mixture was stirred for 15 min, then was filtered through celite®, and the filter pad was washed thoroughly with THF followed by 5% CH₃OH/CHCl₃. The filtrate was concentrated to give the title compound (15.24 g, 83%) as a waxy light yellow solid: MS (ES) *m/e* 125 (M + H)⁺.

15 b) 2-Amino-5-bromo-3-(hydroxymethyl)pyridine

To a solution of 2-amino-3-(hydroxymethyl)pyridine (13.0 g, 116.0 mmole) in CH₂Cl₂ (300 mL) at RT was added NBS (22.71 g, 127.6 mmole). After stirring at RT for 45 min the reaction solution was concentrated and the residue was dissolved in CHCl₃. The resulting suspension was filtered and the filtrate was concentrated to a dark oil.
20 Purification on silica gel (EtOAc) afforded the title compound (78%, 18.36 g) as a tan solid: MS (ES) *m/e* 204 (M + H)⁺.

c) Benzyl (E)-3-[6-amino-5-(hydroxymethyl)pyridin-3-yl]acrylate

According to the procedure of Preparation 2 (a), except substituting 2-amino-3-(hydroxymethyl)-5-bromopyridine (1.10 g, 5.42 mmole) for 2-amino-5-bromopyridine, the
25 title compound (1.25 g, 81%) was prepared as an off-white solid: MS (ES) *m/e* 285 (M + H)⁺.

d) (E)-3-[6-Amino-5-(hydroxymethyl)pyridin-3-yl]acrylic acid

30 According to the procedure of Preparation 2 (b) except substituting benzyl-(E)-3-[6-amino-5-(hydroxymethyl)pyridin-3-yl]acrylate (1.10 g, 5.42 mmole) for benzyl (E)-3-(6-aminopyridin-3-yl)acrylate, the title compound (0.68 g, 65%) was prepared as an off-white solid: MS (ES) *m/e* 194 (M + H)⁺.

Preparation 16Preparation of 6-bromo-3,4-dihydro-1H-1,8-naphthyridin-2-one

5 a) 2-Amino-5-bromo-3-(bromomethyl)pyridine hydrobromide

A solution of 2-amino-5-bromo-3-hydroxymethylpyridine (5.00 g, 24.6 mmole), from Preparation 14 (b), in 48% aqueous HBr (50 mL), was heated at reflux for 12 hrs. The reaction was concentrated and toluene was used to azeotrope the residual H₂O. The resulting light brown solid was placed under high vacuum overnight and used directly.

10

b) Methyl (±)-6-bromo-2-oxo-1,2,3,4-tetrahydro-1H-1,8-naphthyridine-3-carboxylate

To a solution of sodium methoxide (20.57 mL, 25% wt in CH₃OH) in CH₃OH (75 mL) was added dimethyl malonate (11.87 g, 89.9 mmole). After 30 min the 2-amino-5-bromo-3-(bromomethyl)pyridine hydrobromide salt prepared above was added to the methoxide solution and the reaction was stirred at RT overnight. The reaction slurry was concentrated to dryness under vacuum and then suspended in 1:1 H₂O/Et₂O. The remaining solids were filtered and washed with H₂O then with hexanes to afford the title compound (4.08 g, 58 %) as a white solid after drying: MS (ES) *m/e* 286 (M + H)⁺.

15

20 c) 6-Bromo-3,4-dihydro-1H-1,8-naphthyridin-2-one

To a solution of methyl (±)-6-bromo-2-oxo-1,2,3,4-tetrahydro-1H-1,8-naphthyridine-3-carboxylate (2.00 g, 7.0 mmole) in CH₃OH (75 mL) was added 1.0 M NaOH (30 mL). The reaction was heated to reflux for 4 hrs and then cooled to RT. The reaction was neutralized with 1.0 M HCl (30 mL) then was heated at reflux overnight. The reaction slurry was concentrated to dryness and the residues was suspended in 95:5 CHCl₃/CH₃OH. The solids were removed by filtration and the filtrate was concentrated to afford the title compound (1.40 g, 88%) as an off-white solid: MS (ES) *m/e* 228 (M + H)⁺.

25

Preparation 17

30

Preparation of (E)-3-[6-amino-5-[(2-hydroxyethylamino)carbonyl]pyridin-3-yl]acrylic acid

a) 2-Amino-5-bromo-N-(2-hydroxyethyl)nicotinamide

EDC (2.91 g, 15.2 mmole) was added to a solution 2-amino-5-bromonicotinic acid (3.00 g, 13.8 mmole), ethanolamine (0.93 g, 15.2 mmole), HOBt · H₂O (2.05 g, 15.2 mmole), and diisopropylethylamine (2.64 mL, 15.2 mmole) in DMF (50 mL) at RT and the

35

reaction solution was stirred overnight. The reaction contents were poured into H₂O (200 mL) and the resulting mixture was extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with H₂O and brine and then dried over Na₂SO₄. Concentration of the organic extracts afforded the title compound as a yellow solid which was used without further purification: MS (ES) *m/e* 261 (M + H)⁺.

b) Benzyl (E)-3-[6-amino-5-[(2-hydroxyethylamino)carbonyl]pyridin-3-yl]acrylate

According to the procedure of Preparation 2 (a), except substituting 2-amino-5-bromo-N-(2-hydroxyethyl)nicotinamide (2.70 g, 10.4 mmole) for 2-amino-5-bromopyridine, the title compound (2.67 g, 75%) was prepared as an off-white solid: MS (ES) *m/e* 342 (M + H)⁺.

c) (E)-3-[6-Amino-5-[(2-hydroxyethylamino)carbonyl]pyridin-3-yl]acrylic acid

According to the procedure of Preparation 2 (b), except substituting benzyl (E)-3-[6-amino-5-[(2-hydroxyethylamino)carbonyl]pyridin-3-yl]acrylate (2.67 g, 7.8 mmole) for benzyl (E)-3-(6-aminopyridin-3-yl)acrylate the title compound (1.37 g, 70%) was prepared as an off-white solid: MS (ES) *m/e* 252 (M + H)⁺.

Preparation 18

Preparation of 6-bromo-3-methyl-3,4-dihydro-1H-pyrido[2,3-d]pyrimidin-2-one

a) 2-Amino-5-bromo-3-(methylaminomethyl)pyridine

A solution of 2-amino-5-bromo-3-(hydroxymethyl)pyridine (5.00 g, 24.6 mmole), from Preparation 14 (b), in 48% aqueous HBr (50 mL) was heated at reflux for 12 hrs. The reaction was concentrated and toluene was used to azeotrope the residual H₂O. The resulting light brown solid was placed under high vacuum overnight and used directly.

A solution of the 2-amino-3-(bromomethyl)-5-bromopyridine hydrobromide salt (prepared above) in 40% aqueous methylamine (50 mL) and THF (50 mL) was stirred at RT overnight in a pressure bottle. The reaction solution was concentrated and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with H₂O, dried over Na₂SO₄ and concentrated. Purification on silica gel afforded the title compound (4.25 g, 80 %) as a yellow oil: MS (ES) *m/e* 217 (M + H)⁺.

b) 6-Bromo-3-methyl-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one

To a solution of dimethyl carbonate (2.14 g, 23.7 mmole) and sodium methoxide (1.0 mL, 4.5 mmole, 25% wt in CH₃OH) in CH₃OH (25 mL) was added 2-amino-5-bromo-3-(methylaminomethyl)pyridine (1.0 g, 4.62 mmole). The reaction was heated at 50 °C overnight, diluted with H₂O (1 mL) and concentrated. Toluene was added to the reaction residue and the contents were heated to reflux for 12 hr under a Dean-Stark apparatus. The reaction was cooled to RT, diluted with EtOAc, and washed with H₂O. Purification on silica gel (9:1 CHCl₃/CH₃OH containing 5% NH₄OH) gave the title compound (0.75 g, 67%) as an off-white solid: MS (ES) *m/e* 243 (M + H)⁺.

Preparation 19Preparation of 4-methyl-5-(methylaminomethyl)-4*H*-thieno[3,2-*b*]pyrrolea) Ethyl 4-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate

According to the procedure of Preparation 1 (a), except substituting ethyl 4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (1.30 g, 6.7 mmole, see *J. Het. Chem.* **1984**, 21, 215-217) for ethyl indole-2-carboxylate, the title compound (1.35 g, 97%) was prepared as a yellow solid: MS (ES) *m/e* 210 (M + H)⁺.

b) N,4-Dimethyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

According to the procedure of Preparation 1 (b), except substituting ethyl 4-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (1.35 g, 6.5 mmole) for ethyl-1-methylindole-2-carboxylate, the title compound (1.19 g, 95%) was prepared as a yellow solid: MS (ES) *m/e* 195 (M + H)⁺.

c) 4-Methyl-5-(methylaminomethyl)-4*H*-thieno[3,2-*b*]pyrrole

According to the procedure of Preparation 1 (c), except substituting N,4-dimethyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (0.70 g, 3.6 mmole) for N,1-dimethylindole-2-carboxamide, the title compound (0.60 g, 92%) was prepared as a yellow oil: MS (ES) *m/e* 181 (M + H)⁺.

Preparation 20

Preparation of 3-methyl-2-(methylaminomethyl)indene hydrochloride

5 a) N,3-Dimethylinden-2-carboxamide

EDC (1.53 g, 0.01 mole) was added to a solution of 3-methyl-2-inden-2-carboxylic acid (1.91 g, 0.01 mole), methylamine hydrochloride (0.675 g, 0.01 mole), HOBT · H₂O (1.53 g, 0.01 mole) and triethylamine (4.0 mL, 0.028 mole) in anhydrous DMF (80 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo. The residue was
10 diluted with 5% NaHCO₃ and the resulting white precipitate was collected, washed with water and dried at 50°C in a vacuum oven to afford the title compound (1.6 g, 86%) as a white solid: MS (ES) *m/e* 188.2 (M + H)⁺.

b) 3-Methyl-2-(methylaminomethyl)indene hydrochloride

15 A flame-dried flask was charged with anhydrous THF (15 mL) followed by solid lithium aluminum hydride (760 mg, 0.02 mole) at 0 °C. The mixture was stirred for 15 min, then a solution of N,3-dimethylindene-2-carboxamide (1.5 g, 0.008 mole) in anhydrous THF (20 mL) was added dropwise. When the addition was complete, the reaction was heated at gentle reflux for 30 hr, then was cooled in ice and quenched with
20 H₂O (1.4 mL) and NaF (2.5 g, 0.06 mole). The reaction mixture was stirred for 40 min then was filtered through celite®, and the filter pad was washed with THF. The filtrate was dried over K₂CO₃, filtered and concentrated to an oil, which was dissolved in anhydrous ethyl ether and treated with 4 M HCl in diethyl ether. The precipitated light tan solid was collected by suction filtration and washed with diethyl ether. Drying at 50 °C in a vacuum
25 oven gave the title compound (1.05 g, 80.7%) as a light tan solid: MS (ES) *m/e* 174.2 (M + H)⁺.

Preparation 21

30 Preparation of 2-(methylaminomethyl)indene hydrochloride

a) N-Methylindene-2-carboxamide

According to the procedure of Preparation 20 (a), except substituting 2-inden-carboxylic acid for 3-methyl-2-inden-2-carboxylic acid, the title compound was obtained as
35 a white crystalline solid (1.45 g, 83.3%): MS (ES) *m/e* 174.2 (M + H)⁺.

b) 2-(Methylaminomethyl)indene hydrochloride

According to the procedure of Preparation 20 (b), except substituting N-methylindene-2-carboxamide for N,3-dimethylindene-2-carboxamide, the title compound was obtained as an off-white solid (0.685 g, 87.6%): MS (ES) m/e 160.0 (M + H)⁺.

5

Preparation 22Preparation of 4-methoxy-1-methyl-2-(methylaminomethyl)-1H-indole hydrochloride

10 a) Methyl 4-methoxy-1-methyl-1H-indol-2-carboxylate

NaH (60% dispersion in mineral oil, 0.3 g, 7.3 mmole) was washed with hexane then suspended in anhydrous DMF (16 mL). The mixture was cooled to 0 °C and methyl 4-methoxy-1H-indol-2-carboxylate (1.0 g, 4.87 mmole) was added. The mixture was stirred under argon for 10 min, then MeI (1.3 mL, 20 mmole) was added, and the thick slurry was stirred at RT for 2.5 hr. The reaction was quenched with 10% NH₄Cl (2 mL) and concentrated. The residue was partitioned between H₂O and Et₂O, and the organic layer was dried over MgSO₄ and concentrated to yield the title compound (1.03 g, 96%) as a white solid: MS (ES) m/e 220.2 (M + H)⁺.

20 b) N,1-Dimethyl-4-methoxy-1H-indol-2-carboxamide

A solution of methyl 4-methoxy-1-methyl-1H-indol-2-carboxylate (1.03 g, 4.7 mmole) in 2.0 M methylamine in methanol (40 mL) was sealed in a pressure bottle and heated at 55-60 °C for 60 hr. Concentration in vacuo yielded the title compound (1.05 g, quantitative) as a white solid: MS (ES) m/e 219.2 (M + H)⁺.

25

c) 4-Methoxy-1-methyl-2-(methylaminomethyl)-1H-indole hydrochloride

According to the procedure of Preparation 20 (b), except substituting N,1-dimethyl-4-methoxy-1H-indol-2-carboxamide for N,3-dimethylindene-2-carboxamide, the title compound was obtained as an off white solid (0.72 g, 75%): MS (ES) m/e 205.2 (M + H)⁺.

30

Preparation 23

Preparation of 1,4-dimethyl-2-(methylaminomethyl)-1*H*-indole hydrochloride

5 a) 1,4-Dimethyl-1*H*-indol-2-carboxylic acid

A solution of 1,4-dimethyl-1*H*-indole (0.9 g, 6.2 mmole) in anhydrous Et₂O (20 mL) was treated with 2.5 M n-BuLi in hexanes (5.0 mL, 12 mmole) and the reaction was heated at reflux for 15 hr. The dark reaction mixture was poured into a slurry of excess crushed dry ice in Et₂O, and the mixture was allowed to stand for 1 hr. Water (10 mL) was added, the layers separated, and the aqueous layer was filtered through celite®. The clear filtrate was acidified with 2.0 N HCl to pH 2, and the precipitate was collected and dried to afford the title compound (0.29 g, 26.4%) as an off-white solid: MS (ES) *m/e* 190.2 (M + H)⁺.

15 b) N,1,4-Trimethyl-1*H*-indol-2-carboxamide

According to the procedure in Preparation 20 (a), except substituting 1,4-dimethyl-1*H*-indole-2-carboxylic acid for 3-methyl-2-indene-2-carboxylic, the title compound was obtained (0.184 g, 91%): MS (ES) *m/e* 203.2 (M + H)⁺.

20 c) 1,4-Dimethyl-2-(methylaminomethyl)-1*H*-indole hydrochloride

According to the procedure in Preparation 20 (b), except substituting N,1,4-trimethyl-1*H*-indole-2-carboxamide for N,3-dimethylindene-2-carboxamide, the title compound was obtained (0.13 g, 65%): MS (ES) *m/e* 189.2 (M + H)⁺.

25 Preparation 24

Preparation of 2-(cyclopropylamino)-1-methyl-1*H*-indole

30 a) 2-(Cyclopropylamino)-1-methyl-1*H*-indole

To a solution of 1-methylindole-2-carboxaldehyde (1.5 g, 10 mmole), cyclopropylamine (1.14 g, 20 mmole), and glacial acetic acid (0.6 mL, 10 mmole) in MeOH (30 mL) was added NaBH₃CN (0.69 g, 11 mmole). The reaction was stirred at RT overnight, then was concentrated in vacuo. The residue was diluted with 10% NaOH and extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated. Flash chromatography on silica gel (3% MeOH/CH₂Cl₂) gave the title compound (1.3 g, 65%) as a semi-solid: MS (ES) *m/e* 201 (M + H)⁺.

Preparation 25Preparation of 5-fluoro-2-(methylaminomethyl)-1H-indole

5

a) Ethyl 5-fluoro-1-methyl-1H-indole-2-carboxylate

According to the procedure of Preparation 1 (a), except substituting ethyl 5-fluoro-indole-2-carboxylate for the ethyl-indole-2-carboxylate, the title compound (3.3 g, 100%) was prepared as a white solid: MS (ES) *m/e* 222 (M + H)⁺.

10

b) N,1-Dimethyl-5-fluoro-1H-indole-2-carboxamide

According to the procedure of Preparation 1 (b), except substituting ethyl 5-fluoro-1-methyl-1H-indole-2-carboxylate for the ethyl 1-methyl-1H-indole-2-carboxylate, the title compound (2.1 g, 68%) was prepared as a white solid: MS (ES) *m/e* 207 (M + H)⁺.

15

c) 5-Fluoro-2-(methylaminomethyl)-1H-indole

According to the procedure of Preparation 1 (c), except substituting N,1-dimethyl-5-fluoro-1H-indole-2-carboxamide for the N,1-dimethyl-1H-indole-2-carboxamide, the title compound (1.5 g, 78%) was prepared as a white solid: MS (ES) *m/e* 193 (M + H)⁺.

20

Preparation 26Preparation of 3-(methylaminomethyl)quinoline

25

a) 3-(Methylaminomethyl)quinoline

A solution of 3-quinolinecarboxaldehyde (1.5 g, 10 mmole), 2.0 M CH₃NH₂/MeOH (10 mL, 20 mmole), glacial AcOH (0.6 mL, 10 mmole), and NaBH₃CN (0.35 g, 11 mmole) in MeOH (20 mL) was stirred at RT overnight, then was concentrated in vacuo. The residue was diluted with 5% NaOH and extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated. Flash chromatography on silica gel (10% MeOH/CH₂Cl₂) gave the title compound (0.83 g, 24%) as a slightly yellow viscous oil: MS (ES) *m/e* 173 (M + H)⁺.

30

Preparation 27

Preparation of 2-(methylaminomethyl)benzofuran

5 a) N-Methylbenzofuran-2-carboxamide

To a solution of 2-benzofurancarboxylic acid (1.62 g, 10 mmole), methylamine hydrochloride (0.79 g, 11 mmole), triethylamine (3.1 mL, 22 mmole), and HOBt · H₂O (1.5 g, 11 mmole) in DMF (30 mL) was added EDC (2.1 g, 11 mmole). The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with 5% NaHCO₃ and
10 extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated. Flash chromatography on silica gel (3% MeOH/CH₂Cl₂) gave the title compound (1.75 g, 100%) as white solid: MS (ES) *m/e* 176 (M + H)⁺.

b) 2-(Methylaminomethyl)benzofuran

15 To a solution of 1.0 M BH₃/THF (30 mL, 30 mmole) at 0 °C was added N-methylbenzofuran-2-carboxamide (1.75 g, 10 mmole). The reaction mixture was allowed to warm to RT, then was heated at reflux overnight. The reaction was cooled to 0 °C and excess methanol was added. The resulting solution was concentrated in vacuo and the
20 residue was purified by flash chromatography on silica gel (3% MeOH/CH₂Cl₂). The title compound (0.2 g, 12%) was obtained as a white solid: MS (ES) *m/e* 162 (M + H)⁺.

Preparation 28

Preparation of 1-methyl-2-(propylaminomethyl)-1H-indole

25

a) 1-Methyl-N-cyclopropylindole-2-carboxamide

According to the procedure of Preparation 27 (a), except substituting 1-methyl-1H-indole-2-carboxylic acid (3.5 g, 20 mmole) for 2-benzofurancarboxylic acid, and substituting cyclopropylamine for methylamine hydrochloride, the title compound (2.1 g,
30 49%) was prepared as white solid: MS (ES) *m/e* 215 (M + H)⁺.

b) 1-Methyl-2-(propylaminomethyl)-1H-indole

To a solution of 1-methyl-N-cyclopropylindole-2-carboxamide (2.1 g, 9.8 mmole) in dry THF (40 mL) was added dropwise a solution of 1.0 M LiAlH₄ in THF (2.2 mL, 22
35 mmole). The reaction mixture was heated at reflux overnight, then was cooled and quenched with 10% NaOH. The mixture was filtered and the filtrate was concentrated in

vacuo. Flash chromatography on silica gel (5% MeOH/CH₂Cl₂) gave the title compound (0.65 g, 33%) as a viscous oil: MS (ES) *m/e* 203 (M + H)⁺.

Preparation 29

5

Preparation of 5-bromo-2-(methylamino)pyridine and 5-bromo-2-(dimethylamino)pyridine

a) 5-Bromo-2-(methylamino)pyridine and 5-bromo-2-(dimethylamino)pyridine

To a suspension of NaH (60% dispersion in mineral oil, 0.44 g, 11 mmole) in dry
10 DMF (40 mL) was added solid 2-amino-5-bromopyridine (1.73 g, 10 mmole) in portions
over 5-10 min. Gas evolution was allowed to subside between additions. The resulting
amber mixture was stirred for 15 min, then methyl iodide (0.61 mL, 10 mmole) was added
all at once. The reaction mixture was stirred at RT overnight, then was concentrated in
vacuo. The residue was diluted with 5% NH₄Cl (30 mL) and the mixture was extracted
15 with CH₂Cl₂. The combined organic extracts were washed with brine, dried (MgSO₄), and
concentrated. Flash chromatography on silica gel (3% MeOH/CH₂Cl₂) separated the
products. 5-Bromo-2-(methylamino)pyridine (0.60 g, 32 %) was obtained as a semisolid:
TLC (3% MeOH/CH₂Cl₂) R_f 0.35; MS (ES) *m/e* 187 (M + H)⁺. 5-Bromo-2-
(dimethylamino)pyridine (0.70 g, 34%) was obtained as a semisolid: TLC (3%
20 MeOH/CH₂Cl₂) R_f 0.77; MS (ES) *m/e* 201 (M + H)⁺.

Preparation 30

Preparation of (E)-3-[6-(methylamino)pyridin-3-yl]acrylic acid

25

a) Benzyl (E)-3-[6-(methylamino)pyridin-3-yl]acrylate

According to the procedure of Preparation 2 (a), except substituting 5-bromo-2-
(methylamino)pyridine for 2-amino-5-bromopyridine, the title compound (0.52 g, 60%)
was prepared as a white solid: MS (ES) *m/e* 269 (M + H)⁺.

30

b) (E)-3-[6-(Methylamino)pyridin-3-yl]acrylic acid

According to the procedure of Preparation 2 (b), except substituting benzyl (E)-3-
[6-(methylamino)pyridin-3-yl]acrylate for benzyl (E)-3-(6-aminopyridin-3-yl)acrylate, the
title compound (0.15 g, 43%) was prepared as a white solid: MS (ES) *m/e* 179 (M + H)⁺.

35

Preparation 31Preparation of (E)-3-[6-(dimethylamino)pyridin-3-yl]acrylic acid

5 a) Benzyl (E)-3-[6-(dimethylamino)pyridin-3-yl]acrylate

According to the procedure of Preparation 2 (a), except substituting 5-bromo-2-(dimethylamino)pyridine for 2-amino-5-bromopyridine, the title compound (0.82 g, 84%) was prepared as a white solid: MS (ES) *m/e* 283 (M + H)⁺.

10 b) (E)-3-[6-(Dimethylamino)pyridin-3-yl]acrylic acid

According to the procedure of Preparation 2 (b), except substituting benzyl (E)-3-[6-(dimethylamino)pyridin-3-yl]acrylate for benzyl (E)-3-(6-aminopyridin-3-yl)acrylate, the title compound (0.20 g, 36%) was prepared as a white solid: MS (ES) *m/e* 193 (M + H)⁺.

15

Preparation 32Preparation of (E)-3-(6-methylpyridin-3-yl)acrylic acid

20 a) Benzyl (E)-3-(6-methylpyridin-3-yl)acrylic acid

According to the procedure of Preparation 2 (a), except substituting 5-bromo-2-methylpyridine for 2-amino-5-bromopyridine, the title compound (0.85 g, 34%) was prepared as a white solid: MS (ES) *m/e* 253 (M + H)⁺.

25 b) (E)-3-(6-Methylpyridin-3-yl)acrylic acid

According to the procedure of Preparation 2 (b), except substituting benzyl (E)-3-(6-methylpyridin-3-yl)acrylic acid for benzyl (E)-3-(6-aminopyridin-3-yl)acrylate, the title compound (0.18 g, 33%) was prepared as a white solid: MS (ES) *m/e* 164 (M + H)⁺.

30

Preparation 33Preparation of 2-(methylaminomethyl)-1H-indole

a) N-Methyl-1H-indol-2-carboxamide

35

A suspension of ethyl indole-2-carboxylate (25.30 g, 133.7 mmole) in 40% aqueous CH₃NH₂ (400 mL) was stirred at RT. The flask was tightly stoppered to keep the material

inside the flask. As the reaction proceeded the product began to precipitate. The reaction was stirred at RT for 3 days, then was concentrated to remove approximately 200 mL of the solvent. The remaining residue was diluted with H₂O (500 mL), and the solid was collected by suction filtration and washed with H₂O. Drying under high vacuum left the
5 title compound (21.50 g, 92%) as a light yellow solid: MS (ES) *m/e* 175 (M + H)⁺.

b) 2-(Methylaminomethyl)-1*H*-indole

A solution of LiAlH₄ in THF (1.0 M, 250 mL, 250 mmole) was slowly added via syringe to a solution of N-methyl-1*H*-indol-2-carboxamide (21.50 g, 12.34 mmole) in
10 anhydrous THF (100 mL). Gas was evolved during the addition of the first 50 mL of LiAlH₄ solution. When the addition was complete, the resulting light yellow solution was heated at gentle reflux. After 23 hr, the reaction was cooled in ice and quenched by the sequential dropwise addition of H₂O (9.5 mL), 1.0 N NaOH (20 mL), and H₂O (28.5 mL). The mixture was stirred for 15 min, then was filtered through celite®, and the filter pad
15 was washed thoroughly with THF. The filtrate was concentrated and the residue was flash chromatographed on silica gel (10% MeOH/CHCl₃ containing 0.5% conc. NH₄OH). The title compound (10.10 g, 51%) was obtained as a light yellow oil: MS (ES) *m/e* 161 (M + H)⁺.

20

Preparation 34

Preparation of 1-ethyl-2-(methylaminomethyl)-1*H*-indole

a) 2-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1*H*-indole

25 N-(Benzyloxycarbonyloxy)succinimide (17.10 g, 68.6 mmole) was added to a solution of 2-(methylaminomethyl)-1*H*-indole (10.00 g, 62.4 mmole), from Preparation 33, and triethylamine (9.60 mL, 68.6 mmole) in DMF (100 mL) at RT. The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and the mixture was extracted with ethyl acetate. The combined extracts were dried over
30 K₂CO₃ and concentrated. Flash chromatography on silica gel (20% ethyl acetate/hexanes) gave the title compound (14.80 g, 80%) as an off-white solid: MS (ES) *m/e* 295 (M + H)⁺.

b) 2-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1-ethyl-1*H*-indole

35 NaH (60% dispersion in mineral oil, 0.25 g, 7.1 mmole) was added portionwise, allowing for gas evolution, to a solution of 2-[N-(benzyloxycarbonyl)-N-methylaminomethyl]-1*H*-indole (1.40 g, 4.75 mmole) in DMF (35 mL) at 0 °C. When the

NaH addition was complete, ethyl iodide (0.42 mL, 5.2 mmole) was added at 0 °C. The reaction was stirred at 0 °C for 15 minutes then at RT overnight. The reaction was diluted with water and extracted with ethyl acetate. The combined extracts were dried over K₂CO₃ and concentrated to afford the title compound (1.30 g, 87%) as an orange solid:

5 MS (ES) *m/e* 323 (M + H)⁺.

e) 1-Ethyl-2-(methylaminomethyl)-1*H*-indole

2-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1-ethyl-1*H*-indole (1.30 g, 4.0 mmole) was added to a suspension of Pearlman's catalyst (about 0.30 g) in MeOH at RT in a Parr flask. The reaction was placed under 50 p.s.i. of H₂ and shaken for 8 hr. The mixture was filtered through celite® and the filter pad was washed with MeOH. The filtrate was concentrated to afford the title compound (0.75 g, 100%) as a light yellow solid: MS (ES) *m/e* 189 (M + H)⁺.

15 Preparation 35

Preparation of 1-methyl-3-(methylaminomethyl)-1*H*-indole (Method A)

a) Methyl 1-methyl-1*H*-indole-3-carboxylate

20 NaH (60% dispersion in mineral oil, 8.56 g, 214.0 mmole) was added portionwise, allowing for gas evolution, to a solution of methyl 1*H*-indole-3-carboxylate (25.00 g, 142.7 mmole) in DMF (350 mL) at 0 °C. When the NaH addition was complete, methyl iodide (44.4 mL, 713.5 mmole) was added at 0 °C. The reaction was stirred at 0 °C for 15 minutes then at RT overnight. The reaction was diluted with water and extracted with ethyl acetate.
25 The combined extracts were dried over K₂CO₃ and concentrated to afford the title compound (26.00 g, 96%) as an orange solid: MS (ES) *m/e* 190 (M + H)⁺.

b) N,1-Dimethyl-1*H*-indole-3-carboxamide

A suspension of methyl 1-methyl-1*H*-indole-3-carboxylate (4.30 g, 22.74 mmole) in 40% aqueous CH₃NH₂ (400 mL) was stirred at RT. The flask was tightly stoppered to keep the material inside the flask. As the reaction proceeded the product began to precipitate. The reaction was stirred at RT for 3 days, then was concentrated to remove approximately 200 mL of the solvent. The remaining residue was diluted with H₂O (500 mL), and the solid was collected by suction filtration and washed with H₂O. Flash
35 chromatography on silica gel (ethyl acetate) gave the title compound (2.4 g, 56%) as a white solid: MS (ES) *m/e* 189 (M + H)⁺.

c) 1-Methyl-3-(methylaminomethyl)-1*H*-indole

A solution of LiAlH₄ in THF (1.0 M, 5.20 mL, 5.2 mmole) was slowly added via syringe to a solution of N,1-dimethyl-1*H*-indole-3-carboxamide (0.50 g, 2.6 mmole) in anhydrous THF (15 mL). Gas was evolved during the addition of the first 2 mL of LiAlH₄ solution. When the addition was complete, the resulting light yellow solution was heated at gentle reflux. After 23 hr, the reaction was cooled in ice and quenched by the sequential dropwise addition of H₂O (0.5 mL), 1.0 N NaOH (0.5 mL), and H₂O (0.5 mL). The mixture was stirred for 15 min, then was filtered through celite®, and the filter pad was washed thoroughly with THF. The filtrate was concentrated and the residue was flash chromatographed on silica gel (10% MeOH/CHCl₃ containing 0.5% conc. NH₄OH) to afford the title compound (0.30 g, 67%) as a light yellow oil: MS (ES) *m/e* 175 (M + H)⁺.

Preparation 36Preparation of 1-methyl-3-(methylaminomethyl)-1*H*-indole (Method B)

To a solution of 1-methylindole-3-carboxaldehyde (10.0 g, 62.8 mmole) in MeOH (100 mL) was added a solution of 2.0 M CH₃NH₂ in MeOH (126 mL, 252.0 mmole). The reaction was stirred at RT for 2 hrs, then was concentrated to a light yellow oil. This oil was dissolved in EtOH (300 mL), and NaBH₄ (2.38 g, 62.8 mmole) was added. After 2 hrs the reaction was concentrated to a slurry and dissolved in 1.0 N NaOH (75 mL). The aqueous solution was extracted with Et₂O (2 x 200 mL) and the combined organic fractions were dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (9:1 CHCl₃/MeOH containing 5% NH₄OH) and drying in high vacuum left the title compound (10.1 g, 92%) as a faintly yellow oil: MS (ES) *m/e* 175 (M + H)⁺.

Preparation 37Preparation of (E)-3-(6-aminopyridin-3-yl)-2-methylacrylic acid HCl salt and 2-(6-aminopyridin-3-ylmethyl)acrylic acid HCl salt

a) Ethyl (E)-3-(6-aminopyridin-3-yl)-2-methylacrylate and ethyl 2-(6-aminopyridin-3-ylmethyl)acrylate

To a stirred solution of 2-amino-5-bromopyridine (25 g, 140 mmole) in propionitrile (150 mL) was added ethyl methacrylate (50 mL, 400 mmole), DIEA (50 mL,

287 mmole), palladium(II) acetate (1.57 g, 7 mmole), and tri-*o*-tolylphosphine (4.3 g, 14 mmole). The reaction was purged with argon and heated at reflux for 6 hr, then was cooled to RT and concentrated to dryness under vacuum. The residue was taken up in 80% ethyl acetate/hexanes (100 mL), and the solution was filtered through a pad of silica gel, eluting with 80% ethyl acetate/hexanes (400 mL) until all the product was eluted off. The yellowish filtrate was concentrated under vacuum, and the residue was taken up in a small volume of 1:1 Et₂O/petroleum ether. The precipitate which formed was collected and dried under vacuum to give ethyl (E)-3-(6-aminopyridin-3-yl)-2-methylacrylate (10.77 g, 37%) as a pale yellow solid: LCMS (ES) *m/e* 207.0 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, J = 1.7 Hz, 1 H), 7.63 (dd, 1 H), 7.48 (s, 1 H), 6.75 (d, J = 8.8 Hz, 1 H), 5.79 (br s, 2 H), 4.26 (q, 2 H), 2.10 (s, 3 H), 1.34 (t, 3 H). The filtrate was concentrated to dryness and purified by flash chromatography on silica gel (4:1 ethyl acetate/hexanes) to give additional ethyl (E)-3-(6-aminopyridin-3-yl)-2-methylacrylate (0.87 g, 3%) and ethyl 2-(6-aminopyridin-3-ylmethyl)acrylate (5.77 g, 20%) as a yellow oil: LCMS (ES) *m/e* 207.0 (M + H)⁺; ¹H NMR (300 MHz, CDCl₃) δ 7.86 (d, J = 2.1 Hz, 1 H), 7.32 (dd, 1 H), 6.53 (d, J = 8.5 Hz, 1 H), 6.21 (d, J = 1.8 Hz, 1 H), 5.48 (d, J = 1.4 Hz, 1 H), 4.17 (q, 2 H), 3.47 (s, 2 H), 1.27 (t, 3 H).

b) (E)-3-(6-Aminopyridin-3-yl)-2-methylacrylic acid HCl salt

To ethyl (E)-3-(6-aminopyridin-3-yl)-2-methylacrylate (5.0 g, 24.2 mmole) was added HOAc (25 mL) and conc. HCl (25 mL). The reaction was stirred and heated at 100 °C for 6 hr, cooled to RT and concentrated to dryness. The remaining residue was triturated with Et₂O, filtered and dried under vacuum to give the title compound (5.5 g, quantitative) as a white solid: LCMS (ES) *m/e* 179.0 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 8.47 (br s, 2 H), 8.16 (d, J = 1.7 Hz, 1 H), 8.08 (dd, 1 H), 7.42 (s, 1 H), 7.08 (d, J = 9.3 Hz, 1 H), 2.01 (s, 3 H).

c) 2-(6-Aminopyridin-3-ylmethyl)acrylic acid HCl salt

According to the procedure of Preparation 37 (b), except substituting ethyl 2-(6-aminopyridin-3-ylmethyl)acrylate (3.1 g, 15 mmole) for ethyl (E)-3-(6-aminopyridin-3-yl)-2-methylacrylate gave the title compound (3.0 g, 93%) as a white solid: LCMS (ES) *m/e* 179.0 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 8.10 (br s, 2 H), 7.79 (dd, 1 H), 7.78 (s, 1 H), 7.00 (d, J = 9.7 Hz, 1 H), 6.15 (d, J = 1.2 Hz, 1 H), 5.67 (d, J = 1.2 Hz, 1 H), 3.45 (s, 2 H).

Preparation 38Preparation of 2-(methylaminomethyl)naphthalene

5 To a stirred solution of 40 wt% methylamine in H₂O (50 mL, 581 mmole) in THF (50 mL) at 0 °C was added 2-(bromomethyl)naphthalene (10 g, 43 mmole) in one portion. The reaction was allowed to warm to RT and stirred for 16 hr, then was then concentrated under vacuum. The residue was taken up in Et₂O and washed with 1.0 N NaOH then with
10 brine, dried (Na₂SO₄), and concentrated to dryness. Purification by flash chromatography on silica gel (98:2 to 9:1 CHCl₃/methanol containing 5% NH₄OH) gave the title compound (3.95 g, 54%) as a clear oil: ¹H NMR (400 MHz, CDCl₃) δ 7.85 (m, 3 H), 7.79 (s, 1 H), 7.49 (m, 3 H), 3.94 (s, 2 H), 2.53 (s, 3 H).

Preparation 39

15

Preparation of (E)-3-(6-amino-4-methylpyridin-3-yl)acrylic acid HCl salt

a) 2-Amino-5-bromo-4-methylpyridine

To a stirred solution of 2-amino-4-methylpyridine (22 g, 203 mmole) in 48% HBr (200 mL) at 70 °C was added dropwise a solution of 15% H₂O₂ in H₂O (60 mL) over 60
20 minutes. The reaction became slightly exothermic and the oil bath was removed after 15 minutes. The reaction stirred for an additional 1 hr, then was poured into ice (approximately 500 mL). The clear solution was adjusted to pH 4-5 with solid Na₂CO₃ (80 g, 755 mmole), and the resulting thick white suspension was filtered. The filter pad was
25 washed with a small volume of H₂O and pressed dry. Drying under high vacuum gave a 2:3 mixture of 2-amino-5-bromo-4-methylpyridine and 2-amino-3,5-dibromo-4-methylpyridine (27.08 g). Flash chromatography on silica gel (50% ethyl acetate/hexanes then ethyl acetate) gave the title compound (12.11 g, 32%) as a white solid: LCMS (ES) *m/e* 187.2 (M + H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 7.92 (s, 1 H), 6.41 (s, 1 H), 6.03
30 (br s, 2 H), 2.17 (s, 3 H).

b) Ethyl (E)-3-(6-amino-4-methylpyridin-3-yl)acrylate

To a stirred solution of 2-amino-5-bromo-4-methylpyridine (10 g, 54 mmole) in propionitrile (50 mL) was added ethyl acrylate (17 mL, 157 mmole), DIEA (19 mL, 106
35 mmole), palladium(II) acetate (0.61 g, 2.7 mmole) and tri-*o*-tolylphosphine (1.64 g, 5.4 mmole). The reaction was purged with argon and heated at reflux for 6 hr, then was cooled

to RT and concentrated to dryness under vacuum. The resulting residue was taken up in ethyl acetate and filtered through a pad of silica gel. The filtrate was concentrated and the remaining residue was triturated with 1:1 Et₂O/petroleum ether (50 mL), filtered, and dried under vacuum to give the title compound (6.50 g, 59%) as a pale yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ 8.31 (s, 1 H), 7.66 (d, J = 16.0 Hz, 1 H), 6.40 (br s, 2 H), 6.32 (d, J = 16.0 Hz, 1 H), 6.28 (s, 1 H), 4.15 (q, 2 H), 2.24 (s, 3 H), 1.24 (t, 3 H).

c) (E)-3-(6-Amino-4-methylpyridin-3-yl)acrylic acid HCl salt

To ethyl (E)-3-(6-amino-4-methylpyridin-3-yl)acrylate (1.50 g, 7.3 mmole) was added HOAc (15 mL) and conc. HCl (15 mL). The solution was stirred at 100 °C for 10 hr, cooled to RT, and concentrated to dryness. Trituration with Et₂O, filtration and drying under vacuum gave the title compound (1.65 g, quantitative) as a white solid: LCMS (ES) *m/e* 179.2 (M + H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 8.37 (s, 1 H), 8.28 (br s, 3 H), 7.51 (d, J = 16.0 Hz, 1 H), 6.86 (s, 1 H), 6.46 (d, J = 16.0 Hz, 1 H), 2.41 (s, 3 H).

Preparation 40

Preparation of 1,3-dimethyl-2-(methylaminomethyl)-1*H*-indole

a) 1,3-Dimethyl-1*H*-indole

To a stirred solution of 3-methylindole (15.0 g, 114 mmole) in dry DMF (200 mL) was added NaH (60% dispersion in oil, 5.0 g, 125 mmole) in portions. Gas evolution was observed. The mixture was stirred for 30 min, then iodomethane (8 mL, 129 mmole) was added in one portion. The reaction became exothermic and was cooled in an ice bath.

After 16 hr at RT, the reaction was concentrated under vacuum and the residue was taken up in ethyl acetate. The solution was washed with H₂O then with brine, dried (MgSO₄), and concentrated to dryness. Purification by short path distillation under vacuum (bp 88-92°C, 0.5 mmHg) gave the title compound (16.10 g, 97%) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, J = 7.9 Hz, 1 H), 7.35 (d, J = 8.2 Hz, 1 H), 7.13 (t, 1 H), 7.06 (s, 1 H), 7.00 (t, 1 H), 3.71 (s, 3 H), 2.24 (s, 3 H).

b) 1,3-Dimethyl-1*H*-indole-2-carboxaldehyde

To a stirred solution of phosphorus oxychloride (7.0 mL, 75 mmole) in DMF (25 mL) was added dropwise a solution of 1,3-dimethylindole (12.0 g, 83 mmole) in dry DMF (6.0 mL). The reaction was stirred at RT for 2 hr then was poured onto ice. The mixture was basified with a solution of NaOH (13.2 g, 330 mmole) in H₂O (44 mL), then was

extracted with Et₂O (2x 50 mL). The combined organic layers were washed with brine, dried (MgSO₄), and concentrated under vacuum. Flash chromatography on silica gel (10% ethyl acetate/hexanes) gave the title compound (13.03 g, 91%) as an off-white solid: LCMS (ES) *m/e* 174.2 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃) δ 10.16 (s, 1 H), 7.68 (d, J = 8.1 Hz, 1 H), 7.42 (t, 1 H), 7.32 (d, J = 8.5 Hz, 1 H), 7.15 (t, 1 H), 4.04 (s, 3 H), 2.63 (s, 3 H).

c) 1,3-Dimethyl-2-(methylaminomethyl)-1*H*-indole

To 1,3-dimethyl-1*H*-indole-2-carboxaldehyde (13.0 g, 75 mmole) was added a solution of 2.0 M methylamine in methanol (150 mL, 300 mmole) and HOAc (4.3 mL, 75 mmole). The solution was stirred at RT for 4 hr, then was cooled to 0 °C, and sodium cyanoborohydride (5.0 g, 80 mmole) was added portionwise over 5 min. The reaction was then allowed to warm to RT. After 16 hr, the reaction was concentrated under vacuum and the residue was taken up in Et₂O. The solution was washed with 1.0 N NaOH then with brine, dried (Na₂SO₄), and concentrated to dryness. Flash chromatography on silica gel (95:5 CHCl₃/methanol containing 5% NH₄OH) gave the title compound (7.34 g, 52%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, J = 7.8 Hz, 1 H), 7.26 (d, J = 7.8 Hz, 1 H), 7.20 (t, 1 H), 7.09 (t, 1 H), 3.88 (s, 2 H), 3.76 (s, 3 H), 2.46 (s, 3 H), 2.32 (s, 3 H), 1.36 (br s, 1 H).

Preparation 41

Preparation of 6-bromo-2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]-1,3-oxazine

a) 2-Amino-3-(hydroxymethyl)pyridine

To a stirred solution of 2-aminonicotinic acid (20 g, 145 mmole) in dry THF (200 mL) under argon was added 1.0 M LiAlH₄ in THF (300 mL, 300 mmole) carefully, portionwise, through a reflux condenser, over 4 hr. The reaction became exothermic and refluxed without external heating. After the addition was complete, the reaction was heated at reflux for an additional 16 hr, then was cooled to 0 °C and carefully quenched by sequential addition of H₂O (12 mL), 15% NaOH in H₂O (12 mL), and H₂O (35 mL). The resulting thick suspension was stirred for 1 hr, then was filtered through a pad of celite®. The filter pad was rinsed with THF (300 mL), and the filtrate was concentrated to dryness to give the title compound (17.04 g, 95%) as a pale yellow waxy solid: LCMS (ES) *m/e* 125.1 (M + H)⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.84 (dd, 1 H), 7.37 (m, 1 H), 6.53 (dd, 1 H), 5.65 (br s, 2 H), 5.16 (t, 1 H), 4.34 (d, J = 4.6 Hz, 2 H).

b) 2-Amino-5-bromo-3-(hydroxymethyl)pyridine

To a stirred solution of 2-amino-3-(hydroxymethyl)pyridine (15.0 g, 121 mmole) in HOAc (300 mL) at RT was added bromine (6.2 mL, 121 mmole) dropwise over 1 hr. A suspension formed after approximately 15 min. After the addition, the reaction was stirred for an additional 1 hr, then was concentrated under vacuum. The residue was taken up in 1.0 M Na₂CO₃ (500 mL), and the solution was extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated to dryness. The resulting residue was triturated with a small volume of petroleum ether, filtered and dried under vacuum to give the title compound (18.45 g, 75%) as a beige solid: LCMS (ES) *m/e* 203.2 (M + H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 7.89 (d, J = 2.3 Hz, 1 H), 7.52 (s, 1 H), 5.92 (br s, 2 H), 5.29 (br s, 1 H), 4.30 (s, 2 H).

c) 6-Bromo-2-oxo-1,4-dihydro-2H-pyrido[2,3-d]-1,3-oxazine

To a stirred solution of 2-amino-5-bromo-3-(hydroxymethyl)pyridine (3.0 g, 15 mmole) in methanol (30 mL) was added dimethyl carbonate (5 mL, 60 mmole) and sodium methoxide (25 wt% solution in methanol, 4 mL, 17.4 mmole). The reaction was heated at reflux for 18 hr, cooled to RT, and concentrated to dryness. The remaining residue was triturated with saturated aqueous NH₄Cl (50 mL), filtered, washed with cold H₂O (50 mL), and dried under vacuum to give the title compound (1.75 g, 51%) as a beige solid: LCMS (ES) *m/e* 229.0 (M + H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 10.90 (s, 1 H), 8.31 (s, 1 H), 7.90 (s, 1 H), 5.31 (s, 2 H).

Preparation 42Preparation of 3-methyl-2-(methylaminomethyl)benzo[b]thiophene

To a stirred solution of 3-methylbenzo[b]thiophene-2-carboxaldehyde (0.5 g, 2.8 mmole) in methanol (15 mL) was added 2.0 M methylamine in methanol (6 mL, 12 mmole) and HOAc (0.32 mL, 5.7 mmole). The reaction was stirred at RT for hr, then sodium cyanoborohydride (0.2 g, 3 mmole) was added in one portion. After stirring for an additional 16 hr the reaction was concentrated to dryness. The residue was taken up in Et₂O and washed with 1.0 N NaOH then with brine, dried (Na₂SO₄), and concentrated under vacuum. Purification by flash chromatography on silica gel (95:5 CHCl₃/methanol containing 5% NH₄OH) gave the title compound (0.30 g, 56%) as a yellow oil: ¹H NMR

(400 MHz, CDCl₃) δ 7.77 (d, J = 7.8 Hz, 1 H), 7.62 (d, J = 7.9 Hz, 1 H), 7.34 (t, 1 H), 7.28 (t, 1 H), 3.99 (s, 2 H), 2.49 (s, 3 H), 2.34 (s, 3 H), 1.77 (br s, 1 H).

Preparation 43

5

Preparation of 2-(methylaminomethyl)benzothiophene

a) N-methyl benzothiophene-2-carboxamide

To a stirred solution of 2.0 M methylamine in THF (60 mL) and THF (60 mL) was added dropwise at 0 °C a solution of benzothiophene-2-carbonyl chloride (10.8 g, 55 mmole) in THF (50 mL) over 15 minutes. After the addition the reaction was allowed to warm to RT then was concentrated under vacuum. Trituration with a cold solution of 4:1 H₂O/methanol (50 mL), filtration, and drying under vacuum gave the title compound (10.35 g, 98%) as a white solid: MS (ES) *m/e* 191.9 (M + H)⁺.

15

b) 2-(Methylaminomethyl)benzothiophene

To a stirred suspension of N-methyl benzothiophene-2-carboxamide (10.0 g, 52 mmole) in dry THF (75 mL) under argon was added a solution of 1.0 M LiAlH₄ in THF (135 mL, 135 mmole) over 15 minutes. The reaction quickly became clear and was heated at reflux for 2 days. After cooling to 0 °C the reaction was carefully quenched with the sequential addition of H₂O (5.1 mL), 15% NaOH in H₂O (5.1 mL), and H₂O (15.3 mL). The mixture was filtered through a pad of celite® and the filter pad was rinsed with Et₂O (50 mL). The filtrate was concentrated to afford the title compound (9.11 g, 99%) as a pale yellow oil which solidified in the freezer: ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, J = 7.3 Hz, 1 H), 7.72 (d, J = 7.3 Hz, 1 H), 7.33 (m, 2 H), 7.17 (s, 1 H), 4.06 (s, 2 H), 2.53 (s, 3 H), 1.56 (br s, 1 H).

25

Preparation 44

Preparation of 2-methyl-3-(methylaminomethyl)indole

To a solution of 2-methylindole-3-carboxaldehyde (10.00 g, 62.84 mmole) in MeOH (100 mL) was added 2 M CH₃NH₂ in MeOH (200 mL). After stirring for 3 hours at RT, the reaction solution was concentrated to a yellow oil which solidified under vacuum. This solid was dissolved in ethanol (350 mL) and NaBH₄ (2.38 g, 62.8 mmole) was added. The reaction was stirred at RT for 6 hours, then was concentrated under

35

vacuum. The remaining residue was diluted with saturated aqueous Na_2CO_3 (50 mL) and extracted with EtOAc (2 x 200 mL). The organic phase was separated, washed with brine, and dried over Na_2SO_4 . Flash chromatography on silica gel (9:1 $\text{CHCl}_3/\text{MeOH}$ containing 5% NH_4OH) and drying under high vacuum gave the title compound (6.88 g, 63%) as a faintly yellow viscous solid: MS (ES) m/e 175 ($\text{M} + \text{H}$)⁺.

Preparation 45

Preparation of 5-bromo-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one

To a solution of 2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one (5.00 g, 33.3 mmole) in HOAc (100 mL) was added Br_2 (2.6 mL, 50.0 mmole). After stirring for 48 hours at RT, the reaction solution was concentrated to an orange solid, which was suspended in 1 N NaOH (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 . Flash chromatography on silica gel (9:1 $\text{CHCl}_3/\text{MeOH}$ containing 5% NH_4OH) and drying under high vacuum gave the title compound (5.49 g, 72%) as a yellow solid: MS (ES) m/e 230 ($\text{M} + \text{H}$)⁺.

Preparation 46

Preparation of 5-bromo-2-acetylaminopyrimidine

To a solution of 5-bromo-2-aminopyrimidine (2.0 g, 11.5 mmole) in CH_2Cl_2 (75 mL) at RT was added 2,6-lutidine (2.7 mL, 23.0 mmole) followed by acetyl chloride (0.99 g, 12.6 mmole). After stirring for 8 hours, the reaction solution was concentrated under vacuum. The remaining residue was dissolved EtOAc (200 mL), washed with H_2O (100 mL) and brine, and dried over Na_2SO_4 . Flash chromatography on silica gel (95:5 $\text{CHCl}_3/\text{MeOH}$) and drying under high vacuum gave the title compound (1.74 g, 70%) as a yellow solid: MS (ES) m/e 217 ($\text{M} + \text{H}$)⁺.

Preparation 47Preparation of 1-methyl-2-(methylamino methyl)-6-methoxy-1H-indole

5 a) Methyl-1-methyl-6-methoxy-1H-indole-2-carboxylate

According to the procedure of Preparation 1 (a), except substituting methyl-6-methoxyindole-2-carboxylate for ethyl indole-2-carboxylate, the title compound (90%) was prepared as a tan solid: MS (ES) m/e 220.2 (M + H)⁺.

10 b) N,1-Dimethyl-6-methoxy-1H-indole-2-carboxamide

According to the procedure of Preparation 1 (b), except substituting methyl-1-methyl-6-methoxy-1H-indole-2-carboxylate for ethyl-1-methyl-1H-indole-2-carboxylate, the title compound (95%) was prepared as an off-white solid: MS (ES) m/e 219.2 (M + H)⁺ and 437.4 (2M + H)⁺.

15

c) 1-Methyl-2-(methylamino methyl)-6-methoxy-1H-indole

According to the procedure of Preparation 1 (c), except substituting N,1-dimethyl-6-methoxy-1H-indole-2-carboxamide for N,1-dimethyl-1H-indole-2-carboxamide, the title compound (76%) was prepared as a light gray solid: MS (ES) m/e 205.2 (M + H)⁺, 409.4 (2M + H)⁺.

20

Preparation 48Preparation of 1,7-dimethyl-3-(methylaminomethyl)-1H-indole

25

a) 1,7-Dimethyl-1H-indole

According to the procedure of Preparation 1 (a), except substituting 7-methylindole for ethyl indole-2-carboxylate, the title compound (89%) was prepared as a tan solid: MS (ES) m/e 146.2 (M + H)⁺.

30

b) 1,7-Dimethyl-1H-indole-3-carboxaldehyde

According to the procedure of Preparation 40 (b), except substituting 1,7-dimethyl-1H-indole for 1,3-dimethylindole, the title compound (82%) was prepared as a light tan solid: MS (ES) m/e 174.2 (M + H)⁺.

35

c) 1,7-Dimethyl-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 40 (c), except substituting 1,7-dimethyl-1*H*-indole-3-carboxaldehyde for 1,3-dimethyl-1*H*-indole-1-carboxaldehyde, the title compound (98%) was prepared as a white, crystalline solid: MS (ES) *m/e* 189.2 (M + H)⁺.

5

Preparation 49Preparation of 1,5-dimethyl-3-(methylaminomethyl)-1*H*-indole10 a) 1,5-Dimethyl-1*H*-indole

According to the method of Preparation 1 (a), except substituting 5-methylindole for ethyl indole-2-carboxylate, the title compound (92%) was prepared as an amber oil: MS (ES) *m/e* 146.2 (M + H)⁺.

15 b) 1,5-Dimethyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 40 (b), except substituting 1,5-dimethyl-1*H*-indole for 1,3-dimethylindole, the title compound (82%) was prepared as a light tan solid: MS (ES) *m/e* 174.2 (M + H)⁺.

20 c) 1,5-Dimethyl-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 36, except substituting 1,5-dimethyl-1*H*-indole-3-carboxaldehyde for 1,3-dimethyl-1*H*-indole-1-carboxaldehyde, the title compound (89%) was prepared as an oil: MS (ES) *m/e* 189.2 (M + H)⁺.

25

Preparation 50Preparation of 1,6-dimethyl-3-(methylaminomethyl)-1*H*-indole30 a) 1,6-Dimethyl-1*H*-indole

According to the procedure of Preparation 1 (a), except substituting 5-methylindole for ethyl indole-2-carboxylate, the title compound (96%) was prepared as an amber oil: MS (ES) *m/e* 146.2 (M + H)⁺.

b) 1,6-Dimethyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 40 (b), except substituting 1,5-dimethyl-1*H*-indole for 1,3-dimethylindole, the title compound (99%) was prepared as a light tan solid: MS (ES) *m/e* 174.2 (M + H)⁺.

5

c) 1,6-Dimethyl-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 36, except substituting 1,5-dimethyl-1*H*-indole-3-carboxaldehyde for 1,3-dimethyl-1*H*-indole-1-carboxaldehyde, the title compound (95%) was prepared as an oil: MS (ES) *m/e* 189.2 (M + H)⁺.

10

Preparation 51Preparation of 1-benzyl-3-(methylaminomethyl)-1*H*-indole15 a) 3-(Methylaminomethyl)-1*H*-indole

To a solution of indole-3-carboxaldehyde (5.4 g, 34.1 mmole) in MeOH (30 mL) was added a solution of 2.0 M CH₃NH₂ in MeOH (51.3 mL, 102.6 mmole). The reaction was stirred at RT overnight, then was concentrated to a light yellow oil. This oil was dissolved in EtOH (40 mL), and NaBH₄ (1.3 g, 34.1 mmole) was added. After 16 hrs the reaction was concentrated to a slurry and dissolved in 10% Na₂CO₃ (100 mL). The aqueous solution was extracted with EtOAc (2 x 200 mL) and the combined organic fractions were dried over Na₂SO₄ and concentrated. Drying in high vacuum left the title compound (5.2 g, 94%) as a faintly yellow oil: MS (ES) *m/e* 161 (M + H)⁺.

20

25 b) 3-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1*H*-indole

N-(Benzyloxycarbonyloxy)succinimide (8.9 g, 35.7 mmole) was added to a solution of 3-(methylaminomethyl)-1*H*-indole (5.2 g, 32.5 mmole) and triethylamine (5.0 mL, 65.7 mmole) in DMF (100 mL) at RT. The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and the mixture was extracted with ethyl acetate. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (33% ethyl acetate/hexanes) gave the title compound (7.0 g, 74%) as an off-white solid: MS (ES) *m/e* 295 (M + H)⁺.

30

c) 3-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1-benzyl-1*H*-indole

NaH (60% dispersion in mineral oil, 0.15 g, 3.8 mmole) was added portionwise, allowing for gas evolution, to a solution of 3-[N-(benzyloxycarbonyl)-N-

35

methylaminomethyl]-1*H*-indole (0.7 g, 2.5 mmole) in DMF (25 mL) at 0 °C. When the NaH addition was complete, benzyl bromide (1.2 mL, 10.0 mmole) was added at 0 °C. The reaction was stirred at 0 °C for 15 minutes then at RT overnight. The reaction was diluted with water and extracted with ethyl acetate. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (33% ethyl acetate/hexanes) gave the title compound (0.9 g, 93%) as an off white solid: MS (ES) *m/e* 385 (M + H)⁺.

d) 1-Benzyl-3-(methylaminomethyl)-1*H*-indole

3-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1-benzyl-1*H*-indole (0.9 g, 2.3 mmole) was added to a suspension of Pearlman's catalyst (about 0.30 g) in MeOH at RT in a Parr flask. The reaction was placed under 50 p.s.i. of H₂ and shaken for 5 hr. The mixture was filtered through celite® and the filter pad was washed with MeOH. The filtrate was concentrated to afford the title compound (0.5 g, 86%) as a light yellow solid: MS (ES) *m/e* 251 (M + H)⁺.

Preparation 52

Preparation of 2-phenylamino-3-bromopyridine

A mixture of 2,5-dibromopyridine (10.2 g, 43 mmole) in aniline (25 mL) was stirred and heated at reflux for 3 h. The reaction was cooled to RT and most of the aniline was distilled off under vacuum. The remaining residue was taken up in ethyl acetate and the solution was washed with 1.0 N Na₂CO₃ then with brine, dried (Na₂SO₄), and concentrated under vacuum. Trituration with petroleum ether, filtration and drying under vacuum gave the title compound (7.20 g, 67%) as a tan solid: ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, J = 2.4 Hz, 1 H), 7.58 (dd, 1 H), 7.31-7.39 (m, 4 H), 7.11 (m, 1 H), 6.79 (br s, 1 H); MS (ES) *m/e* 249.0 (M + H)⁺.

Preparation 53

Preparation of 1,2-dimethyl-3-(methylaminomethyl)-1*H*-indole

a) 1,2-Dimethylindole-3-carboxaldehyde
A solution of POCl₃ (7.0 mL, 75 mmole) in DMF (100 mL) was stirred for 5 minutes at 0 °C, then 1, 2-dimethylindole (10.0 g, 69 mmole) was added in one portion. The reaction was allowed to warm to RT and stirred for 4 h. The thick slurry was poured

into ice water (300 mL) and the flask was rinsed with additional water (50 mL). The aqueous mixture was basified with a solution of NaOH (13.2 g, 330 mmole) in H₂O (50 mL), and the thick suspension was filtered to collect the solid. This was washed with water and dried under vacuum to give the title compound (11.59 g, 97%) as an off-white solid:

5 ¹H NMR (400 MHz, CDCl₃) δ 10.07 (s, 1 H), 8.09 (d, J = 7.9 Hz, 1 H), 7.54 (d, J = 7.6 Hz, 1 H), 7.21 (dt, 2 H), 3.73 (s, 3 H), 2.70 (s, 3 H).

b) 1,2-Dimethyl-3-(methylinomethyl)-1*H*-indole

10 To 1,2-dimethylindole-3-carboxaldehyde (11.50 g, 66.4 mmole) was added a solution of 2 M methylamine in methanol (100 mL, 200 mmole). The reaction was stirred for 4 h at RT then was concentrated to dryness to afford the crude title compound: ¹H NMR (400 MHz, CDCl₃) δ 8.55 (d, J = 1.4 Hz, 1 H), 8.16 (d, J = 7.5 Hz, 1 H), 7.42 (d, J = 7.8 Hz, 1 H), 7.15 (t, 1 H), 7.07 (t, 1 H), 3.68 (s, 3 H), 3.41 (s, 3 H), 2.55 (s, 3 H).

15 c) 1,2-Dimethyl-3-(methylaminomethyl)-1*H*-indole

1,2-Dimethyl-3-(methylinomethyl)-1*H*-indole was taken up in ethanol (200 mL) and NaBH₄ (2.6 g, 68.7 mmole) was added portionwise with stirring at RT (vigorous gas evolution). After 16 h the reaction was concentrated under vacuum, and the residue was basified with aqueous 1.0 N NaOH (200 mL). The mixture was extracted with Et₂O (250 mL), and the combined Et₂O extracts were washed with brine, dried (Na₂SO₄) and concentrated. Purification by flash chromatography on silica gel (5-10% (5% NH₄OH/MeOH)/CHCl₃) gave the title compound (8.47 g, 68%) as an oil which solidified in the freezer: ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, J = 7.7 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 7.19 (t, 1 H), 7.12 (t, 1 H), 3.93 (s, 2 H), 3.69 (s, 3 H), 2.49 (s, 3 H), 2.45 (s, 3 H).

25

Preparation 54

Preparation of 3-(methylaminomethyl)benzo[*b*]thiophene

30 To a stirred solution of 2 M methylamine in methanol (75 mmole, 150 mmole) was added benzo[*b*]thiophen-3-carboxaldehyde (5.3 g, 33 mmole) and HOAc (4.3 mL, 75 mmole). The reaction was stirred at RT for 1 h, then NaBH₃CN (2.1 g, 33 mmole) was added portionwise over 5 minutes. The reaction was stirred for an additional 16 h then was concentrated under vacuum. The residue was taken up in Et₂O (300 mL) and washed with
35 1.0 N NaOH (300 mL) then with brine, dried (Na₂SO₄), and concentrated. Purification by flash chromatography on silica gel (5% (5% NH₄OH/MeOH)/CHCl₃) gave the title

compound (2.81 g, 48%) as a brownish oil: ^1H NMR (400 MHz, CDCl_3) δ 7.87 (2d, 2 H), 7.40 (m, 2 H), 7.32 (s, 1 H), 4.02 (s, 2 H), 2.56 (s, 3 H), 1.5 (br s, 1 H).

Preparation 55

5

Preparation of 5-bromo-2,2'-dipyridylamine

Bromine (3.0 mL, 58.2 mmole) was added dropwise over 15 minutes to a stirred solution of 2,2'-dipyridylamine (10 g, 58.4 mmole) in HOAc (100 mL). The reaction quickly became a thick suspension.. After 2 h the reaction was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (0.5% (5% $\text{NH}_4\text{OH}/\text{MeOH})/\text{CHCl}_3$). The resulting residue was triturated with hexane and dried under vacuum gave the title product (1.77 g, 12%) as an off-white solid: ^1H NMR (400 MHz, CDCl_3) δ 9.88 (s, 1 H), 8.31 (s, 1 H), 8.23 (d, $J = 4.8$ Hz, 1 H), 7.83 (m, 2 H), 7.67 (t, 1 H), 7.62 (d, $J = 8.4$ Hz, 1 H), 6.90 (t, 1 H); MS (ES) m/e 250.0 ($\text{M} + \text{H}$) $^+$. 5,5'-dibromo-2,2'-dipyridylamine (4.04 g, 21%) was also isolated as a white solid after trituration with hexane and drying under vacuum: ^1H NMR (400 MHz, CDCl_3) δ 10.08 (s, 1 H), 8.32 (d, $J = 2.5$ Hz, 2 H), 7.88 (dd, 2 H), 7.68 (d, $J = 9.0$ Hz, 2 H); MS (ES) m/e 328.0 ($\text{M} + \text{H}$) $^+$.

20

Preparation 56

Preparation of 2-(methylaminomethyl)-3-methylbenzo[*b*]thiophene

According to the procedures of Preparation 53 (b) and (c), except substituting 3-methylbenzo[*b*]thiophene-2-carboxaldehyde (7.40 g, 42 mmole) for 1,2-dimethylindole-3-carboxaldehyde, the title compound (6.02 g, 75%) was prepared as a pale yellow oil which solidified in the freezer: ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 7.8$ Hz, 1 H), 7.62 (d, $J = 7.9$ Hz, 1 H), 7.34 (t, 1 H), 7.28 (t, 1 H), 3.99 (s, 2 H), 2.49 (s, 3 H), 2.34 (s, 3 H), 1.77 (br s, 1 H).

30

Preparation 57Preparation of 2-methyl-3-(methylaminomethyl)benzo[*b*]thiophene5 a) 2-Methylbenzo[*b*]thiophene-3-carboxaldehyde

SnCl₄ (20 mL, 67 mmole) was added over 5 min to a stirred solution of 2-methylbenzo[*b*]thiophene (5.0 g, 33.7 mmole) in CH₂Cl₂ (75 mL) at 0 °C under argon. After 15 minutes, dichloromethyl methyl ether (3.7 mL, 41 mmole) was added. The reaction became a yellowish colored suspension. The reaction was allowed to warm to RT and stirred for 16 h, then was poured onto ice water (200 mL). The aqueous mixture was acidified with 1.0 N HCl (100 mL) and stirred until the suspension dissolved. The organic phase was separated, dried (MgSO₄), and concentrated under vacuum. Purification by flash chromatography on silica gel (10% ethyl acetate/hexane) gave the title compound (5.83 g, 98%) as a white crystalline solid: ¹H NMR (400 MHz, CDCl₃) δ 10.38 (s, 1 H), 8.61 (d, J = 8.1 Hz, 1 H), 7.77 (d, J = 8.0 Hz, 1 H), 7.48 (t, 1 H), 7.39 (t, 1 H), 2.93 (s, 3 H).

b) 2-Methyl-3-(methylaminomethyl)benzo[*b*]thiophene

According to the procedures of Preparation 53 (b) and (c), except substituting 2-methylbenzo[*b*]thiophene-3-carboxaldehyde (5.0 g, 28.4 mmole) for 1,2-dimethylindole-3-carboxaldehyde, the title compound (4.89 g, 90%) was prepared as an oil which solidified in the freezer: ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 7.9 Hz, 1 H), 7.75 (d, J = 7.9 Hz, 1 H), 7.37 (t, 1 H), 7.29 (t, 1 H), 3.95 (s, 2 H), 2.60 (s, 3 H), 2.50 (s, 3 H).

Preparation 58

25

Preparation of 3,4-dimethyl-2-(methylaminomethyl)thieno[2,3-*b*]thiophene

According to the procedure of Preparation 24 (a), except substituting 3,4-dimethylthieno[2,3-*b*]thiophene-2-carboxaldehyde (0.5 g, 2.5 mmole) for the 1-methylindole-2-carboxaldehyde, the title compound (0.28 g, 53%) was prepared as a colorless oil: MS (ES) *m/e* 212 (M + H)⁺.

30

Preparation 59Preparation of 1-methyl-2-(methylaminomethyl)naphthalene

5 a) N,1-Dimethylnaphthalene-2-carboxamide

According to the procedure of Preparation 20 (a), except substituting 1-methylnaphthalene-2-carboxylic acid (*J. Org. Chem.* **1965**, 22, 3869; 0.3 g, 1.6 mmole) for the 3-methyl-2-inden-2-carboxylic acid, the title compound (0.3 g, 94%) was prepared as a white solid: MS (ES) *m/e* 200 (M + H)⁺.

10

b) 1-Methyl-2-(methylaminomethyl)naphthalene

According to the procedure of Preparation 20 (b), except substituting N,1-dimethylnaphthalene-2-carboxamide (0.3 g, 1.5 mmole) for the N,3-dimethylindene-2-carboxamide, the title compound (0.1 g, 36%) was prepared as a colorless oil: MS (ES) *m/e*

15 186 (M + H)⁺.Preparation 60Preparation of 1-methyl-3-(methylaminomethyl)-1H-pyrrolo[2,3-b]pyridine

20

a) 1-Methyl-1H-pyrrolo[2,3-b]pyridine

According to the procedure of Preparation 40 (a), except substituting 7-azaindole (2.28 g, 1.83 mmole) for the 3-methylindole, the title compound (1.4 g, 58%) was prepared as a yellow oil: MS (ES) *m/e* 133 (M + H)⁺.

25

b) 1-Methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxaldehyde

According to the procedure of Preparation 40 (b), except substituting 1-methyl-1H-pyrrolo[2,3-b]pyridine (0.7 g, 5.3 mmole) for the 1,3-dimethylindole, the title compound (0.4 g, 47%) was prepared as a white solid: MS (ES) *m/e* 161 (M + H)⁺.

30

c) 1-Methyl-3-(methylaminomethyl)-1H-pyrrolo[2,3-b]pyridine

According to the procedure of Preparation 40 (c), except substituting 1-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxaldehyde (0.4 g, 2.5 mmole) for the 1,3-dimethyl-1H-indole-2-carboxaldehyde, the title compound (0.2 g, 45%) was prepared as a yellow oil:

35 MS (ES) *m/e* 176 (M + H)⁺.

Preparation 61

Preparation of 2,3-dihydro-8-(methylaminomethyl)-1H-3a-azacyclopenta[a]indene

5 a) 2,3-Dihydro-1H-3a-azacyclopenta[a]indene-8-carboxaldehyde

According to the procedure of Preparation 40 (b), except substituting 2,3-dihydro-1H-3a-azacyclopenta[a]indene (*J. Med. Chem.* **1965**, 8, 700; 0.24 g, 1.53 mmole) for the 1,3-dimethylindole, the title compound (0.17 g, 60%) was prepared as a yellow solid: MS (ES) *m/e* 186 (M + H)⁺.

10

b) 2,3-Dihydro-8-(methylaminomethyl)-1H-3a-azacyclopenta[a]indene

According to the procedure of Preparation 40 (c), except substituting 2,3-dihydro-1H-3a-azacyclopenta[a]indene-8-carboxaldehyde (0.17 g, 0.92 mmole) for the 1,3-dimethyl-1H-indole-2-carboxaldehyde, the title compound (0.1 g, 54%) was prepared as a

15 yellow oil: MS (ES) *m/e* 201 (M + H)⁺.

The following examples illustrate methods for preparing the biologically active compounds of this invention from intermediate compounds such as those described in the foregoing Preparations.

20

Example 1

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide

25

EDC (0.70 g, 3.7 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.61 g, 3.7 mmole), 1-methyl-2-(methylaminomethyl)-1H-indole (0.65 g, 3.7 mmole), HOBt · H₂O (0.50 g, 3.7 mmole), and triethylamine (0.52 mL, 3.7 mmole) in DMF (30 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo.

30 The residue was diluted with 5% NaHCO₃ and extracted with CH₂Cl₂. The combined organic extracts were washed with brine and dried over MgSO₄. Flash chromatography on silica gel (3% MeOH/CH₂Cl₂) gave a colorless semisolid which was triturated with Et₂O and dried. The title compound (1.0 g, 83%) was obtained as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.20 (br s, 1 H), 7.45 - 7.70 (m, 3 H), 7.00 - 7.30 (m, 3 H), 6.69 (d, J = 15.4

35 Hz, 1 H), 6.30 - 6.50 (m, 2 H), 4.89 (s, 2 H), 4.67 (br s, 2 H), 3.68 (s, 3 H), 3.01 (s, 3 H);

MS (ES) m/e 321 ($M + H$)⁺. Anal. Calcd for $C_{19}H_{20}N_4O \cdot 0.40 H_2O$: C, 69.66; H, 6.40; N, 17.10. Found: C, 69.99; H, 6.27; N, 16.84.

Example 2

5

Preparation of (E)-3-(4-aminophenyl)-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide

EDC (218 mg, 1.14 mmole) was added to a solution of 4-aminocinnamic acid hydrochloride (220 mg, 1.10 mmole), 1-methyl-2-(methylaminomethyl)-1H-indole (0.20 g, 1.15 mmole), HOBt \cdot H₂O (154 mg, 1.14 mmole), and triethylamine (0.20 mL, 1.43 mmole) in DMF (20 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo. The residue was diluted with 5% NaHCO₃ and extracted with CH₂Cl₂. The combined organic extracts were washed with brine (2 x 30 mL) and dried over MgSO₄. Flash chromatography on silica gel (3% MeOH/CH₂Cl₂) gave the title compound (68 mg, 19%) as a yellow foam: ¹H NMR (360 MHz, DMSO-d₆, 330K) δ 7.46 (d, J = 7.8 Hz, 1 H), 7.42 (d, J = 15.3 Hz, 1 H), 7.37 (d, J = 8.3 Hz, 1 H), 7.32 (d, J = 8.5 Hz, 2 H), 7.06 - 7.15 (m, 1 H), 6.94 - 7.03 (m, 1 H), 6.81 (d, J = 15.3 Hz, 1 H), 6.58 (d, J = 8.5 Hz, 2 H), 6.33 (s, 1 H), 5.25 (br s, 2 H), 4.85 (s, 2 H), 3.70 (s, 3 H), 3.02 (s, 3 H); MS (ES) m/e 320 ($M + H$)⁺. Anal. Calcd for $C_{20}H_{21}N_3O \cdot 0.20 H_2O$: C, 74.37; H, 6.68; N, 13.01. Found: C, 74.21; H, 6.60; N, 12.80.

Example 3

Preparation of (E)-N-Methyl-N-(1-methyl-1H-indol-2-ylmethyl)-3-(pyridin-3-yl)acrylamide

EDC (0.22 g, 1.14 mmole) was added to a solution of *trans*-3-(3-pyridyl)acrylic acid (0.17 g, 1.14 mmole), 1-methyl-2-(methylaminomethyl)-1H-indole (0.20 g, 1.15 mmole), and HOBt \cdot H₂O (0.15 g, 1.11 mmole) in DMF (10 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo. The residue was diluted with 5% NaHCO₃ and extracted with CH₂Cl₂. The combined organic extracts were washed with brine and dried over MgSO₄. Flash chromatography on silica gel (3% MeOH/CH₂Cl₂) followed by preparative TLC (3% MeOH/CH₂Cl₂) gave the title compound (0.14 g, 40%) as a white solid: ¹H NMR (360 MHz, CDCl₃) indicated an approximately 8:1 mixture of amide rotamers; for the major rotamer: δ 8.79 (s, 1 H), 8.59 (d, J = 3.9 Hz, 1 H), 7.84 (d, J

= 7.6 Hz, 1 H), 7.76 (d, J = 15.5 Hz, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.38 - 7.48 (m, 2 H), 7.19 - 7.27 (m, 1 H), 7.08 - 7.17 (m, 1 H), 6.98 (d, J = 15.5 Hz, 1 H), 6.51 (s, 1 H), 4.94 (s, 2 H), 3.73 (s, 3 H), 3.09 (s, 3 H); MS (ES) *m/e* 306 (M + H)⁺. Anal. Calcd for C₁₉H₁₉N₃O · 0.20 H₂O: C, 73.86; H, 6.33; N, 13.60. Found: C, 73.52; H, 6.32; N, 13.43.

5

Example 4

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indazol-3-ylmethyl)acrylamide

10

a) (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indazol-3-ylmethyl)acrylamide
EDC (230 mg, 1.2 mmole) was added to a solution (E)-3-(6-aminopyridin-3-yl)acrylic acid (164 mg, 1.0 mmole), 1-methyl-3-(methylaminomethyl)-1*H*-indazole (210 mg, 1.2 mmole), HOBT · H₂O (162 mg, 1.2 mmole), and Et₃N (0.28 mL, 2.0 mmole) in dry
15 DMF (5 mL) at RT. After 18 hr the mixture was concentrated. Flash chromatography on silica gel (5% EtOH/EtOAc) gave the title compound (238 mg, 74%) as a white foam: ¹H NMR (400 MHz, CDCl₃) δ 8.24 (m, 1 H), 7.90 (m, 1 H), 7.65 (m, 2 H), 7.35 (m, 2 H), 7.09 (m, 1 H), 6.73 (m, 1 H), 6.50 (m, 1 H), 5.04 (s, 2 H), 4.83 (bs, 2 H), 4.04 (s, 3 H), 3.10 (s, 3 H); MS (ES) *m/e* 322 (M + H)⁺.

20

Example 5

Preparation of (E)-3-(3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

25

a) (E)-3-(3,4-Dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

EDC (230 mg, 1.2 mmole) was added to a solution (E)-3-(3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl)acrylic acid (206 mg, 1.0 mmole), 1-methyl-2-(methylaminomethyl)-1*H*-indole (209 mg, 1.2 mmole), HOBT · H₂O (162 mg, 1.2 mmole), and Et₃N (0.21 mL, 1.5 mmole) in dry DMF (5 mL) at RT. After 18 hr the mixture was concentrated. Flash chromatography on silica gel (5% EtOH/EtOAc) gave the title compound (238 mg, 66%) as a yellow solid: ¹H NMR (400 MHz, d⁶-DMSO) δ 7.99-6.95 (m, 8 H), 6.40 (s, 1 H), 4.82 (s, 2 H), 4.11 (bs, 2 H), 3.72 (bs, 3 H), 3.67 (bs, 2 H), 3.08 (s, 3
35 H); for minor rotomer δ 6.15 (s, 1 H), 5.02 (s, 2 H), 2.96 (s, 3 H); MS (ES) *m/e* 363 (M + H)⁺.

Example 6

5 Preparation of (E)-N-methyl-N-[(1-methyl-1*H*-indol-2-yl)methyl]-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

a) (E)-N-Methyl-N-[(1-methyl-1*H*-indol-2-yl)methyl]-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

EDC (203 mg, 1.06 mmole) was added to a solution (E)-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid (180 mg, 0.88 mmole), 1-methyl-2-(methylaminomethyl)-1*H*-indole (185 mg, 1.06 mmole), HOBt · H₂O (143 mg, 1.06 mmole), and Et₃N (0.31 mL, 2.2 mmole) in dry DMF (5 mL) at RT. After 18 hr the mixture was concentrated. Flash chromatography on silica gel (10% EtOH/EtOAc) gave the title compound (222 mg, 70%) as a yellow solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.99-6.82 (m, 8 H), 6.40 (s, 1 H), 4.82 (s, 2 H), 3.67 (m, 2 H), 3.29 (m, 3 H), 3.07 (m, 3 H), 2.73 (m, 2 H), 1.77 (m, 2 H); for minor rotomer δ 6.16 (s, 1 H), 5.00 (s, 2 H); MS (ES) *m/e* 361 (M + H)⁺.

Example 7

20 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(thieno[2,3-*b*]thiophen-2-yl)methyl)acrylamide

a) (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(thieno[2,3-*b*]thiophen-2-yl)methyl)acrylamide

EDC (230 mg, 1.2 mmole) was added to a solution (E)-3-(6-aminopyridin-3-yl)acrylic acid (164 mg, 1.0 mmole), 2-(methylaminomethyl)thieno[2,3-*b*]thiophene (220 mg, 1.2 mmole), HOBt · H₂O (162 mg, 1.2 mmole), and Et₃N (0.35 mL, 2.5 mmole) in dry DMF (5 mL) at RT. After 18 hr the mixture was concentrated. Flash chromatography on silica gel (5% EtOH/EtOAc) gave the title compound (138 mg, 42%) as a tan solid: ¹H NMR (400 MHz, *d*⁶-DMSO) δ 8.15 (d, *J* = 2.0 Hz, 1 H), 7.84 (bs, 1 H), 7.57 (d, *J* = 5.2 Hz, 1 H), 7.43 (d, *J* = 15.2 Hz, 1 H), 7.27 (m, 2 H), 6.44 (m, 2 H), 4.75 (s, 2 H), 3.13 (s, 3 H); for minor rotomer δ 5.00 (s, 2 H), 2.95 (s, 3 H); MS (ES) *m/e* 330 (M + H)⁺.

Example 8

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(thieno[3,2-*b*]thiophen-2-ylmethyl)acrylamide

5

a) (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(thieno[3,2-*b*]thiophen-2-ylmethyl)acrylamide

EDC (230 mg, 1.2 mmole) was added to a solution (E)-3-(6-aminopyridin-3-yl)acrylic acid (164 mg, 1.0 mmole), 2-(methylaminomethyl)thieno[3,2-*b*]thiophene (220 mg, 1.2 mmole), HOBt · H₂O (162 mg, 1.2 mmole), and Et₃N (0.35 mL, 2.5 mmole) in dry DMF (5 mL) at RT. After 18 hr the mixture was diluted with H₂O and extracted with EtOAc (3x). The combined organic layers were dried (MgSO₄) and concentrated. The solid was taken up in 1:1 MeOH/H₂O and filtered. The filtrate was concentrated to approximately 1/3 volume. The precipitate was collected by filtration, washed with H₂O, and dried *in vacuo* to afford the title compound (139 mg, 42%) as a light tan solid: ¹H NMR (400 MHz, d⁶-DMSO) δ 8.15 (d, J = 2.0 Hz, 1 H), 7.83 (bd, 1 H), 7.61 (d, J = 5.2 Hz, 1 H), 7.40 (m, 3 H), 6.45 (m, 2 H), 4.75 (s, 2 H), 3.13 (s, 3 H); for minor rotomer δ 5.00 (s, 2 H), 2.95 (s, 3 H); MS (ES) *m/e* 330 (M + H)⁺.

10
15

20

Example 9

Preparation of (E)-3-(3*H*-imidazo[4,5-*b*]pyridin-6-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

25 a) (E)-3-(3*H*-Imidazo[4,5-*b*]pyridin-6-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

EDC (230 mg, 1.2 mmole) was added to a solution (E)-3-(3*H*-imidazo[4,5-*b*]pyridin-6-yl)acrylic acid (189 mg, 1.0 mmole), 1-methyl-2-(methylaminomethyl)-1*H*-indole (209 mg, 1.2 mmole), HOBt · H₂O (162 mg, 1.2 mmole), and Et₃N (0.28 mL, 2.0 mmole) in dry DMF (5 mL) at RT. After 18 hr the mixture was diluted with H₂O. The title compound (193 mg, 56%) was collected as a white solid by filtration, washed with H₂O, and dried *in vacuo*: ¹H NMR (400 MHz, d⁶-DMSO) δ 8.72 (s, 1 H), 8.50 (s, 2 H), 7.68 (d, J = 15.4 Hz, 1 H), 7.45 (m, 3 H), 7.13 (m, 1 H), 7.01 (m, 1 H), 6.43 (s, 1 H), 4.87 (s, 2 H), 3.70 (s, 3 H), 3.15 (s, 3 H); for minor rotomer δ 8.68 (s, 1 H), 8.47 (s, 2 H), 6.19 (s, 1 H), 5.10 (s, 2 H), 3.74 (s, 3 H), 3.01 (s, 3 H); MS (ES) *m/e* 346 (M + H)⁺.

30
35

Example 10

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(6-methyl-6H-thieno[2,3-b]pyrrol-5-ylmethyl)acrylamide

5

a) (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(6-methyl-6H-thieno[2,3-b]pyrrol-5-ylmethyl)acrylamide

EDC (132 mg, 0.69 mmole) was added to a solution (E)-3-(6-aminopyridin-3-yl)acrylic acid (95 mg, 0.58 mmole), 6-methyl-5-(methylaminomethyl)-6H-thieno[2,3-b]pyrrole (142 mg, 0.69 mmole), HOBt · H₂O (93 mg, 0.69 mmole), and Et₃N (0.16 mL, 1.16 mmole) in dry DMF (3 mL) at RT. After 18 hr the mixture was diluted with H₂O and extracted with EtOAc (3x). The combined organic layers were dried (MgSO₄) and concentrated. The residue was taken up in MeOH and collected by filtration to give the title compound (65 mg, 34%) as a yellow solid: ¹H NMR (400 MHz, d⁶-DMSO) δ 8.15 (s, 1 H), 7.81 (d, J = 8.1 Hz, 1 H), 7.43 (d, J = 15.2 Hz, 1 H), 6.96 (m, 2 H), 6.43 (m, 3 H), 4.70 (s, 2 H), 3.61 (s, 3 H), 3.00 (s, 3 H); for minor rotomer δ 4.87 (s, 2 H), 2.90 (s, 3 H); MS (ES) *m/e* 327 (M + H)⁺.

15

Example 11

20

Preparation of (E)-3-(2-aminopyrimidin-5-yl)-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide

According to the procedure of Example 1, except substituting (E)-3-(2-aminopyrimidin-5-yl)acrylic acid (0.50 g, 3.0 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, the title compound (0.86 g, 89%) was prepared as an off-white solid: MS (ES) *m/e* 322 (M + H)⁺.

25

Example 12

30

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(benzo[*b*]thiophen-2-ylmethyl)-N-methylacrylamide

According to the procedure of Example 1, except substituting 2-(methylaminomethyl)benzo[*b*]thiophene (0.47 g, 2.68 mmole) for 1-methyl-2-

35

(methyaminomethyl)indole, the title compound (0.71 g, 91%) was prepared as an off-white solid: MS (ES) m/e 324 ($M + H$)⁺.

Example 13

5

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-2-butenamide

10 According to the procedure of Example 1, except substituting (E)-3-(6-aminopyridin-3-yl)-2-methylacrylic acid (0.40 g, 2.24 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, the title compound (0.65 g, 87%) was prepared as an off-white solid: MS (ES) m/e 335 ($M + H$)⁺.

Example 14

15

Preparation of (E)-3-(6-amino-2-methylpyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

20 According to the procedure of Example 1, except substituting (E)-3-(6-amino-2-methylpyridin-3-yl)acrylic acid (0.40 g, 2.24 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, the title compound (0.70 g, 94%) was prepared as an off-white solid: MS (ES) m/e 335 ($M + H$)⁺.

Example 15

25

Preparation of (E)-3-(6-amino-5-methylpyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

30 According to the procedure of Example 1, except substituting (E)-3-(6-amino-5-methylpyridin-3-yl)acrylic acid (1.00 g, 5.62 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, the title compound (1.78 g, 95%) was prepared as an off-white solid: MS (ES) m/e 335 ($M + H$)⁺.

Example 16Preparation of (E)-3-[6-acetylamino]pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

5

To a stirred suspension of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-[(1-methyl-1*H*-indol-2-yl)methyl]acrylamide (0.50 g, 1.56 mmole) and NaHCO₃ (0.51 g, 6.09 mmole) in THF (75 mL) was added acetic anhydride (0.38 g, 3.74 mmole). The reaction was heated at reflux for 24 hrs and then concentrated. The remaining residue was extracted with EtOAc and purified on silica gel (95:5 CHCl₃/CH₃OH) to give the title compound (0.54 g, 96 %) as an off-white solid: MS (ES) *m/e* 363 (M + H)⁺.

10

Example 17

15 Preparation of (E)-3-(6-amino-5-methylpyridin-3-yl)-N-(benzo[*b*]thiophen-2-ylmethyl)-N-methylacrylamide

According to the procedure of Example 1, except substituting (E)-3-(6-amino-5-methylpyridin-3-yl)acrylic acid (0.40 g, 2.24 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, and substituting 2-(methylaminomethyl)benzo[*b*]thiophene (0.44 g, 2.47 mmole) for 1-methyl-2-(methylaminomethyl)indole, the title compound (0.69 g, 91%) was prepared as an off-white solid: MS (ES) *m/e* 338 (M + H)⁺.

20

Example 18

25

Preparation of (E)-3-(6-amino-5-methylpyridin-3-yl)-N-methyl-N-(naphthalen-2-ylmethyl)acrylamide

According to the procedure of Example 1, except substituting (E)-3-(6-amino-5-methylpyridin-3-yl)acrylic acid (0.40 g, 2.24 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, and substituting 2-(methylaminomethyl)naphthalene (0.42 g, 2.47 mmole) for 1-methyl-2-(methylaminomethyl)indole, the title compound (0.65 g, 87%) was prepared as an off-white solid: MS (ES) *m/e* 332 (M + H)⁺.

30

Example 19Preparation of (E)-3-[6-acetylamino-5-methylpyridin-3-yl]-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide

5 According to the procedure of Example 16, except substituting (E)-3-(6-amino-5-methylpyridin-3-yl)-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide (0.47 g, 1.4 mmole) for (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]acrylamide, the title compound (0.49 g, 93%) was prepared as an off-white solid:
10 MS (ES) m/e 377 ($M + H$)⁺.

Example 20

15 Preparation of (E)-3-[6-amino-5-(hydroxymethyl)pyridin-3-yl]-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide

According to the procedure of Example 1, except substituting (E)-3-[6-amino-5-(hydroxymethyl)pyridin-3-yl]acrylic acid (0.40 g, 2.1 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, the title compound (0.56 g, 77%) was prepared as an off-white solid: MS
20 (ES) m/e 351 ($M + H$)⁺.

Example 21

25 Preparation of (E)-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

a) N-Methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide

To a solution of 1-methyl-2-(methylaminomethyl)indole (0.78 g, 4.5 mmole), from Preparation 1, and triethylamine (1.4 mL, 10.0 mmole) in CH₂Cl₂ (50 mL) at 5 °C was
30 added acryloyl chloride (0.41 mL, 4.95 mmole). After 45 min, the reaction solution was poured onto H₂O and the layers were separated. The organic phase was dried over Na₂SO₄ and concentrated to afford the title compound as a yellow oil. This was used directly without further purification.

b) (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Preparation 2 (a), except substituting N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (0.90 g, 3.96 mmole) for benzyl acrylate, and substituting 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (0.60 g, 2.64 mmole) for 2-amino-5-bromopyridine, the title compound (0.85 g, 86%) was prepared as an off-white solid: MS (ES) *m/e* 375 (M + H)⁺.

Example 22

10

Preparation of (E)-3-[6-amino-5-[(2-hydroxyethylamino)carbonyl]pyridin-3-yl]-N-(1-methyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide

According to the procedure of Example 1, except substituting (E)-3-[6-amino-5-[(2-hydroxyethylamino)carbonyl]pyridin-3-yl]acrylic acid (1.35 g, 5.4 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, the title compound (1.95 g, 89%) was prepared as an off-white solid: MS (ES) *m/e* 408 (M + H)⁺.

Example 23

20

Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)acrylamide

a) N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

To a solution of 1-methyl-2-(methylaminomethyl)indole (0.96 g, 5.5 mmole), from Preparation 1, and triethylamine (1.54 mL, 11.0 mmole) in CH₂Cl₂ (50 mL) at 5 °C was added acryloyl chloride (0.48 mL, 6.0 mmole). After 45 min, the reaction solution was poured onto H₂O and the layers were separated. The organic phase was dried over Na₂SO₄ and concentrated to afford the title compound as a yellow oil. This was used directly without further purification.

b) (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)acrylamide

According to the procedure of Preparation 2 (a), except substituting N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (1.25 g, 5.5 mmole) for benzyl acrylate, and substituting 6-bromo-3-methyl-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one (0.80 g, 3.3

mmole) for 2-amino-5-bromopyridine, the title compound (0.62 g, 49%) was prepared as an off-white solid: MS (ES) m/e 390 ($M + H$)⁺.

Example 24

5

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(4-methyl-4H-thieno[3,2-b]pyrrol-5-ylmethyl)acrylamide

According to the procedure of Example of 1, except substituting 4-methyl-5-(methylaminomethyl)-4H-thieno[3,2-b]pyrrole (0.60 g, 3.3 mmole) for 1-methyl-2-(methylaminomethyl)indole, the title compound (0.90 g, 92%) was prepared as an off-white solid: MS (ES) m/e 327 ($M + H$)⁺.

Example 26

15

Preparation of (E)-3-[6-aminopyridin-3-yl]-N-methyl-N-(3-methyl-1H-inden-2-ylmethyl)acrylamide

EDC (0.383 g, 2.0 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.328 g, 2.0 mmole), 3-methyl-2-(methylaminomethyl)indene hydrochloride (0.420 g, 2.0 mmole), HOBt · H₂O (0.306 g, 2.0 mmole), and triethylamine (0.57 mL, 4.0 mmole) in anhydrous DMF (18 mL) at RT. The reaction was stirred overnight and concentrated in vacuo. The residue was diluted with 5% NaHCO₃ and extracted with CH₂Cl₂. The combined organic extracts were washed with brine and dried over MgSO₄. Flash chromatography on silica gel (3% MeOH/ CH₂Cl₂) gave the title compound (0.33 g, 52%) as a colorless solid: MS (ES) m/e 320.2 ($M + H$)⁺. Anal. Calcd for C₂₀H₂₁N₃O · 0.4 H₂O: C, 73.57; H, 6.72; N, 12.86. Found: C, 73.94; H, 6.92; N, 12.50.

30

Example 27

Preparation of (E)-3-[6-aminopyridin-3-yl]-N-(1H-inden-2-ylmethyl)-N-methylacrylamide

According to the procedure in Example 26, except substituting 2-(methylaminomethyl)indene hydrochloride for 3-methyl-2-(methylaminomethyl)indene hydrochloride, the title compound (0.23 g, 38%) was obtained as an off-white solid: MS

(ES) m/e 306.2 (M + H)⁺. Anal. Calcd for C₁₉H₁₉N₃O · 0.125 H₂O: C, 74.18; H, 6.30; N, 13.64. Found: C, 74.21; H, 6.25; N, 13.27.

Example 28

5

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(4-methoxy-1-methyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide

According to the procedure in Example 26, except substituting 4-methoxy-1-methyl-2-(methylaminomethyl)-1*H*-indole hydrochloride for 3-methyl-2-(methylaminomethyl)indene hydrochloride, the title compound (0.115 g, 68%) was obtained as an off white solid: MS (ES) m/e 351.2 (M + H)⁺. Anal. Calcd for C₂₀H₂₂N₄O₂: C, 68.55; H, 6.32; N, 15.98. Found: C, 68.15; H, 6.33; N, 15.73.

15

Example 29

Preparation of (E)-3-[6-(acetylamino)pyridin-3-yl]-N-methyl-N-(3-methyl-1*H*-inden-2-ylmethyl)acrylamide

To a solution of (E)-3-[6-aminopyridin-3-yl]-N-methyl-N-(3-methyl-1*H*-inden-2-ylmethyl)acrylamide (0.159 g, 0.5 mmole), from Example 26, in anhydrous THF (20 mL) was added NaHCO₃ (0.126 g, 1.5 mmole) followed by acetic anhydride (0.153 g, 0.15 mmole). The mixture was heated at reflux for 40 hr, then was concentrated under vacuum. The residue was partitioned between H₂O and EtOAc, and the organic layer was dried over MgSO₄, filtered and concentrated. The residue was triturated with diethyl ether to give the title compound (0.135 g, 74.8%) as an off-white solid: MS (ES) m/e 362.2 (M + H)⁺. Anal. Calcd for C₂₂H₂₃N₃O₂ · 0.25 H₂O: C, 72.20; H, 6.47; N, 11.47. Found: C, 72.42; H, 6.45; N, 11.07.

Example 30Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1,4-dimethyl-1H-indol-2-ylmethyl)-N-methylacrylamide

5

According to the procedure in Example 26, except substituting 1,4-dimethyl-2-(methylaminomethyl)-1H-indole hydrochloride for 3-methyl-2-(methylaminomethyl)-indene hydrochloride, the title compound (0.088 g, 52.7%) was obtained as an off white solid: MS (ES) *m/e* 335.2 (M + H)⁺. Anal. Calcd for C₂₀H₂₂N₄O · 0.125 H₂O: C, 71.35; H, 6.66; N, 16.64. Found: C, 71.23; H, 6.65; N, 16.67.

10

Example 31Preparation of (E)-N-methyl-N-(3-methyl-1H-inden-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

15

a) N-Methyl-N-(3-methyl-1H-inden-2-ylmethyl)-acrylamide

To a solution of 3-methyl-2-(methylaminomethyl)indene hydrochloride (0.132 g, 0.63 mmole), from Preparation 19, and triethylamine (0.19 g, 1.89 mmole) in CH₂Cl₂ (6 mL) at 0 °C was added a solution of acryloyl chloride (0.06 mL, 0.7 mmole) in CH₂Cl₂ (2 mL). The reaction was stirred at 0 °C for 1 hr, then was poured into water. The layers were separated, and the organic layer was washed with brine, dried over Mg SO₄ and concentrated in vacuo to yield the title compound (0.145 g, quantitative) as an oily solid: MS (ES) *m/e* 228.2 (M + H)⁺.

20

b) (E)-N-Methyl-N-(3-methyl-1H-inden-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

A mixture of 6-bromo-3,4-dihydro-1H-1,8-naphthyridin-2-one (0.096 g, 0.42 mmole), from Preparation 15, and N-methyl-N-(3-methyl-1H-inden-2-ylmethyl)acrylamide (0.141 g, 0.62 mmole) in propionitrile (10 mL) was treated with (*i*-Pr)₂NEt (0.15 mL, 0.08 mmole), palladium acetate (0.014 g, 0.062 mmole), and (*o*-tolyl)₃P (0.025 g, 0.08 mmole), and the resulting mixture was heated at gentle reflux. After 18 hr, the reaction was cooled, filtered through celite®, and concentrated. Flash chromatography on silica gel (2% MeOH/CH₂Cl₂) gave the title compound (0.06 g, 41%) as a glassy solid: MS (ES) *m/e* 374.2 (M + H)⁺. Anal. Calcd for C₂₃H₂₃N₃O₂ · 1.25 H₂O: C, 69.76; H, 6.41; N, 10.61. Found: C, 69.86; H, 6.67; N, 10.51.

25

30

35

Example 32

5 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1-methyl-1*H*-indol-2-ylmethyl)-N-propylacrylamide

10 According to the procedure of Example 1, except substituting 1-methyl-2-(propylaminomethyl)-1*H*-indole (0.2 g, 1 mmole) for 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound (0.14 g, 40%) was prepared as a white solid: MS (ES) *m/e* 349 (M + H)⁺.

Example 33

15 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(5-fluoro-1-methyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide

20 According to the procedure of Example 1, except substituting 5-fluoro-2-(methylaminomethyl)-1*H*-indole (0.192 g, 1 mmole) for 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound (0.1 g, 30%) was prepared as a white solid : MS (ES) *m/e* 339 (M + H)⁺.

Example 34

25 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(naphthalen-1-ylmethyl)acrylamide

30 According to the procedure of Example 1, except substituting N-methyl-1-(methylaminomethyl)naphthalene hydrochloride (0.2 g, 1 mmole) for 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound (0.09 g, 28%) was prepared as a white solid: MS (ES) *m/e* 318 (M + H)⁺.

Example 35Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(benzofuran-2-ylmethyl)-N-methylacrylamide

5

According to the procedure of Example 1, except substituting 2-(methylamino methyl)benzofuran (0.17 g, 1.1 mmole) for 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound (0.10 g, 30%) was prepared as a white solid: MS (ES) *m/e* 308 (M + H)⁺.

10

Example 36Preparation of (E)-N-methyl-3-[6-(methylamino)pyridin-3-yl]-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

15

According to the procedure of Example 1, except substituting (E)-3-[6-(methylamino)pyridin-3-yl]acrylic acid (0.15 g, 0.84 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, the title compound (0.1 g, 37%) was prepared as a white solid: MS (ES) *m/e* 335 (M + H)⁺.

20

Example 37Preparation of (E)-3-[6-(dimethylamino)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

25

According to the procedure of Example 1, except substituting (E)-3-[6-(dimethylamino)pyridin-3-yl]acrylic acid (0.20 g, 1.0 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, the title compound (0.22 g, 63%) was prepared as a white solid: MS (ES) *m/e* 349 (M + H)⁺.

30

Example 38Preparation of (E)-3-(6-aminopyridin-3-yl)-N-cyclopropyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

5

According to the procedure of Example 1, except substituting 2-(cyclopropylamino)-1-methyl-1*H*-indole (0.22 g, 1.1 mmole) for 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound (0.154 g, 53%) was prepared as a white solid: MS (ES) *m/e* 347 (M + H)⁺.

10

Example 39Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(quinolin-3-ylmethyl)acrylamide

15

According to the procedure of Example 1, except substituting 3-(methylaminomethyl)quinoline (0.172 g, 1 mmole) for 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound (0.100 g, 31%) was prepared as a white solid: MS (ES) *m/e* 319 (M + H)⁺.

20

Example 40Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(6-methylpyridine-3-yl)acrylamide

25

According to the procedure of Example 1, except substituting (E)-3-(6-methylpyridin-3-yl)acrylic acid (0.18 g, 1.1 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, the title compound (0.11 g, 31%) was prepared as a white solid: MS (ES) *m/e* 320 (M + H)⁺.

Example 41Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(2-oxopropylamino)pyridin-3-yl]acrylamide

5

To a solution of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (0.12 g, 0.32 mmol), from Example 1, in DMF (1 mL) was added NaH (14 mg, 60% dispersion in oil, 0.35 mmol) and 1-bromo-2,2-dimethoxy-propane (0.05 mL, 0.37 mmol). After 18 h at RT, the reaction was complete by TLC analysis. The solvent was removed under vacuum and the residue was purified by reverse phase preparative HPLC (YMC CombiPrep[®] ODS-A, 10% to 90% CH₃CN/H₂O + 0.1% TFA) to give the title compound (11.6 mg) as a pale yellow oil: ¹H NMR (400 MHz, MeOH-d₄, 2:1 mixture of rotamers, minor rotamer in italics) δ 9.28 and 9.22 (s, 1 H), 8.60 and 8.52 (s, 1 H), 8.25 and 8.15 (d, 1 H), 7.68 (d, *J* = 16 Hz, 1 H), 7.50 (m, 1 H), 7.35 (m, 3 H), 7.15 (m, 1 H), 7.02 (m, 1 H), 6.55 and 6.25 (s, 1 H), 5.05 and 4.95 (s, 2 H), 3.72 and 3.68 (s, 3 H), 3.50 and 3.48 (s, 3 H), 3.35 (s, 2 H), 3.15 and 3.10 (s, 3 H). MS (ES+) *m/e* 376.3 (M + H)⁺. Unreacted (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (68 mg) was also recovered.

20

Example 42Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1*H*-indol-2-ylmethyl)-N-methylacrylamide

EDC (0.30 g, 1.58 mmole) was added to a solution of 3-(6-aminopyridin-3-yl)acrylic acid (0.26 g, 1.58 mmole), 2-(methylaminomethyl)-1*H*-indole (0.23 g, 1.43 mmole), HOBt · H₂O (0.21 g, 1.58 mmole) and diisopropylethylamine (0.51 mL, 2.86 mmole) in DMF (20 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Flash chromatography on silica gel (10% MeOH/CHCl₃) gave the title compound (0.30 g, 68%) as a light yellow solid: MS (ES) *m/e* 307 (M + H)⁺.

30

Example 43Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1-ethyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide

5

EDC (0.84 g, 4.38 mmole) was added to a solution of 3-(6-aminopyridin-3-yl)acrylic acid (0.72 g, 4.38 mmole), 1-ethyl-2-(methylaminomethyl)-1*H*-indole (0.75 g, 3.98 mmole), HOBt · H₂O (0.59 g, 4.38 mmole) and diisopropylethylamine (1.40 mL, 7.96 mmole) in DMF (30 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Flash chromatography on silica gel (5% MeOH/CHCl₃) gave the title compound (0.40 g, 30%) as a light tan solid: MS (ES) *m/e* 335 (M + H)⁺.

15

Example 44Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide

20

EDC (0.35 g, 1.89 mmole) was added to a solution of 3-(6-aminopyridin-3-yl)acrylic acid (0.31 g, 1.89 mmole), 1-methyl-3-(methylaminomethyl)-1*H*-indole (0.30 g, 1.72 mmole), HOBt · H₂O (0.24 g, 1.89 mmole) and diisopropylethylamine (0.60 mL, 3.44 mmole) in DMF (20 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Flash chromatography on silica gel (5% MeOH/CHCl₃) gave the title compound (0.30 g, 55%) as a light yellow solid: MS (ES) *m/e* 321 (M + H)⁺.

25

Example 45

30

Preparation of (E)-3-[6-((E)-but-2-enoylamino)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

35

Crotonic anhydride (0.29 mL, 1.96 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (0.16 g, 0.49 mmole) and sodium bicarbonate (0.20 g, 2.45 mmole) in THF (30 mL) at RT, and the

reaction was heated at reflux under nitrogen. After 48 hr, the reaction was concentrated in vacuo and the residue was diluted with water and extracted with ethyl acetate. The combined extracts were dried over Na₂SO₄ and concentrated in vacuo to afford the title compound (0.10 g, 53%) as a tan solid: MS (ES) *m/e* 389 (M + H)⁺.

5

Example 46

Preparation of (E)-3-[6-(1,3-dioxo-1,3-dihydroisoindol-2-yl)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

10

Phthalic anhydride (0.81 g, 5.48 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (0.44 g, 1.37 mmole) and sodium bicarbonate (0.58 g, 6.85 mmole) in THF (70 mL) at RT, and the reaction was heated at reflux under nitrogen. After 48 hr, the reaction was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (ethyl acetate). The title compound (0.21 g, 33%) was obtained as a white solid: MS (ES) *m/e* 451 (M + H)⁺.

15

Example 47

20

Preparation of (E)-3-[6-[(2-carboxybenzoyl)amino]pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

Phthalic anhydride (0.81 g, 5.48 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (0.44 g, 1.37 mmole) and sodium bicarbonate (0.58 g, 6.85 mmole) in THF (70 mL) at RT, and the reaction was heated at reflux under nitrogen. After 48 hr, the reaction was concentrated in vacuo and the residue was diluted with water and extracted with ethyl acetate. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (10% MeOH/CHCl₃) gave the title compound (0.10 g, 16%) as a light yellow solid: MS (ES) *m/e* 469 (M + H)⁺.

30

Example 48Preparation of (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(propionylamino)pyridin-3-yl]acrylamide

5

Propionic anhydride (0.90 mL, 7.04 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (0.56 g, 1.76 mmole) and sodium bicarbonate (0.74 g, 8.8 mmole) in THF (40 mL) at RT, and the reaction was heated at reflux under nitrogen. After 48 hr, the reaction was concentrated in vacuo and the residue was diluted with water and extracted with ethyl acetate. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (ethyl acetate) gave the title compound (0.35 g, 53%) as a white solid: MS (ES) *m/e* 377 (M + H)⁺.

15

Example 49Preparation of (E)-3-[6-(3-Ethylureido)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

20

Ethyl isocyanate (0.13 mL, 1.68 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (0.27 g, 0.84 mmole) and triethylamine (0.29 mL, 2.1 mmole) in DMF (30 mL) at RT. The reaction was stirred for 6 days, then was concentrated in vacuo, and the residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated. Flash chromatography on silica gel (ethyl acetate) gave the title compound (80 mg, 24%) as a light yellow solid: MS (ES) *m/e* 392 (M + H)⁺.

25

Example 50Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(3-methylureido)pyridin-3-yl]acrylamide

30

Methyl isocyanate (0.18 mL, 3.05 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (0.20 g, 0.61 mmole) and triethylamine (0.17 mL, 1.22 mmole) in DMF (20 mL) at RT. The reaction was stirred for 5 days, then was concentrated in vacuo, and the residue was diluted with

35

water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated. Flash chromatography on silica gel (ethyl acetate) gave the title compound (0.10 g, 43%) as an off white solid: MS (ES) *m/e* 378 (M + H)⁺.

5

Example 51

Preparation of (E)-3-[6-(acetylamino)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide

10

Acetic anhydride (0.12 mL, 1.24 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)-N-(1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide (0.10 g, 0.31 mmole) and sodium bicarbonate (0.13 g, 1.55 mmole) in THF (20 mL) at RT, and the reaction was heated at reflux under nitrogen. After 48 hr, the reaction was concentrated in vacuo and the residue was diluted with water and extracted with ethyl acetate. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (ethyl acetate) gave the title compound (50 mg, 45%) as a white solid: MS (ES) *m/e* 363 (M + H)⁺.

15

20

Example 52

Preparation of (E)-3-(6-aminopyridin-3-yl)-2-methyl-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

25

To a stirred solution of (E)-3-(6-aminopyridin-3-yl)-2-methylacrylic acid HCl salt (0.5 g, 2.3 mmole) in dry 1:1 DMF/CH₂Cl₂ (30 mL) at RT was added 1-methyl-2-(methylaminomethyl)indole (0.42 g, 2.4 mmole), HOBt · H₂O (0.32 g, 2.4 mmole), Et₃N (0.66 mL, 4.7 mmole), and EDC (0.46 g, 2.4 mmole). After stirring for 24 hr the reaction was concentrated to dryness. The residue was taken up in ethyl acetate and the solution was washed with H₂O, dried (Na₂SO₄), and concentrated under vacuum. Flash chromatography on silica gel (4% methanol/CHCl₃) followed by trituration with ethyl acetate/hexane gave the title compound (0.55 g, 75%) as an off-white solid: LCMS (ES) *m/e* 335.2 (M + H)⁺; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.96 (s, 1 H), 7.52 (d, *J* = 7.8 Hz, 1 H), 7.48 (dd, 1 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 7.14 (t, 1 H), 7.03 (t, 1 H), 6.46 (d, *J* = 8.7 Hz, 1 H), 6.43 (s, 1 H), 6.40 (s, 1 H), 6.17 (br s, 2 H).

30

35

Example 53Preparation of 2-(6-aminopyridin-3-ylmethyl)-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide

5

According to the procedure of Example 52, except substituting 2-(6-aminopyridin-3-ylmethyl)acrylic acid HCl salt (0.50 g, 2.3 mmole) for (E)-3-(6-aminopyridin-3-yl)-2-methylacrylic acid HCl salt, the title compound (0.55 g, 75%) was prepared as an off-white solid following purification by flash chromatography on silica gel (4% methanol/CHCl₃):

10 LCMS (ES) *m/e* 335.2 (M + H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 7.75 (d, J = 2.0 Hz, 1 H), 7.50 (d, J = 7.6 Hz, 1 H), 7.38 (d, J = 8.1 Hz, 1 H), 7.22 (dd, 1 H), 7.12 (t, 1 H), 7.01 (t, 1 H), 6.40 (d, J = 8.4 Hz, 1 H), 6.17 (s, 1 H), 5.83 (br s, 2 H), 5.23 (s, 1 H), 5.14 (s, 1 H), 4.73 (s, 2 H), 3.57 (s, 3 H), 3.36 (s, 2 H), 2.82 (s, 3 H).

15

Example 54Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(naphthalen-2-ylmethyl)acrylamide

20

To a stirred solution of (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.30 g, 1.8 mmole) in 1:1 DMF/CH₂Cl₂ (25 mL) was added 2-(methylaminomethyl)naphthalene (0.34 g, 2 mmole), HOBt · H₂O (0.27 g, 2 mmole), Et₃N (0.28 mL, 2 mmole), and EDC (0.38 g, 2 mmole). After stirring at RT for 16 hr the reaction was concentrated under vacuum. The residue was taken up in ethyl acetate and the solution was washed with H₂O, dried

25 (Na₂SO₄) and concentrated to dryness. Purification by flash chromatography on silica gel (4% methanol/CHCl₃), trituration with 1:1 ethyl acetate/hexane, filtration, and drying under vacuum gave the title compound (0.49 g, 81%) as an off-white solid: LCMS (ES) *m/e* 318.0 (M + H)⁺.

30

Example 55Preparation of (E)-3-(6-amino-4-methylpyridin-3-yl)-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide

35

To a stirred solution of (E)-3-(6-amino-4-methylpyridin-3-yl)acrylic acid HCl salt (0.70 g, 3.3 mmole) in 1:1 DMF/CH₂Cl₂ (30 mL) was added Et₃N (0.42 mL, 3 mmole), 1-

5 methyl-2-(methylaminomethyl)indole (0.50 g, 2.9 mmole), HOBt · H₂O (0.41 g, 3 mmole), and DCC (0.70 g, 3 mmole). After stirring at RT for 16 hr the reaction was concentrated under vacuum. The residue was taken up in ethyl acetate and filtered. The filtrate was washed with 1.0 N Na₂CO₃ then with brine, dried (Na₂SO₄), and concentrated under vacuum. Purification by flash chromatography on silica gel (4% methanol/CHCl₃) gave the title compound (0.74 g, 74%) as a pale yellow solid: LCMS (ES) *m/e* 335.2 (M + H)⁺.

Example 56

10 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1,3-dimethyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide

15 To a stirred solution of 1,3-dimethyl-2-(methylaminomethyl)-1*H*-indole (0.6 g, 3.2 mmole) in 1:1 DMF/CH₂Cl₂ (25 mL) was added (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.50 g, 3 mmole), HOBt · H₂O (0.43 g, 3.2 mmole), and DCC (0.66 g, 3.2 mmole). After stirring at RT for 16 hr the reaction was concentrated under vacuum. Purification by flash chromatography on silica gel (3% methanol/CHCl₃) gave the title compound (0.83 g, 83%) as an off-white solid: LCMS (ES) *m/e* 335.4 (M + H)⁺.

Example 57

20

Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]-1,3-oxazin-6-yl)acrylamide

25 a) N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

To a stirred solution of 1-methyl-2-(methylaminomethyl)-1*H*-indole (1.0 g, 5.7 mmole), from Preparation 1, and Et₃N (0.9 mL, 6.4 mmole) in CH₂Cl₂ (50 mL) at 0 °C was added dropwise acryloyl chloride (0.51 mL, 6 mmole) over 5 minutes. The reaction was stirred at 0 °C for 1 hr, then was poured into ice water. The organic phase was separated, washed with brine, dried (MgSO₄), and concentrated to dryness to give the title compound (1.19 g, 91%) as a yellow oil. This was used without further purification: TLC (silica gel, 50% EtOAc/hexanes) R_f = 0.31.

30

b) (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]-1,3-oxazin-6-yl)acrylamide

To a stirred solution of N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (1.19 g, 5.2 mmole) in propionitrile (50 mL) was added 6-bromo-2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]-1,3-oxazine (1.1 g, 4.9 mmole), DIEA (1.75 mL, 10 mmole), palladium(II) acetate (112 mg, 0.5 mmole), and tri-*o*-tolylphosphine (304 mg, 1.0 mmole). The reaction was purged with argon and heated at reflux for 16 hr, then was cooled to RT and concentrated under vacuum. The residue was taken up in CHCl₃ and the solution was filtered through a pad of silica gel (3% methanol/CHCl₃). The filtrate was concentrated and the residue was triturated with ethyl acetate, collected by suction filtration, and dried under vacuum gave the title compound (1.02 g, 55%) as an off-white solid: LCMS (ES) *m/e* 377.4 (M + H)⁺.

Example 58

15

Preparation of (E)-N-(1,3-dimethyl-1*H*-indol-2-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

20

a) N-(1,3-Dimethyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide

25

To a stirred solution of 1,3-dimethyl-2-(methylaminomethyl)indole (1.5 g, 8 mmole), from Preparation 40, and Et₃N (1.12 mL, 8 mmole) in CH₂Cl₂ (75 mL) at 0 °C was added acryloyl chloride (0.65 mL, 8 mmole) dropwise over 5 minutes. The reaction was stirred at 0 °C for 1 hr then was poured into ice water. The organic phase was separated, washed with brine, dried (MgSO₄), and concentrated to dryness to give the title compound (1.7 g, 90%) as a yellow oil. This was used without further purification: TLC silica gel (50% EtOAc/hexanes) R_f = 0.41.

30

b) (E)-N-(1,3-Dimethyl-1*H*-indol-2-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro[1,8]naphthyridin-3-yl)acrylamide

35

To a stirred solution of N-(1,3-dimethyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide (1.7 g, 7 mmole) in propionitrile (50 mL) was added 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (1.16 g, 5.1 mmole), DIEA (1.8 mL, 10.3 mmole), palladium(II) acetate (112 mg, 0.5 mmole), and tri-*o*-tolylphosphine (304 mg, 1.0 mmole). The reaction was purged with argon and heated at reflux for 16 hr, then was cooled to RT and concentrated under vacuum. Purification by flash chromatography on silica gel (5% methanol/CHCl₃),

trituration with ethyl acetate, filtration, and drying under vacuum gave the title compound (1.17 g, 59%) as an off-white solid: LCMS (ES) *m/e* 389.2 (M + H)⁺.

Example 59

5

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(3-methylbenzo[*b*]thiophen-2-ylmethyl)acrylamide

To a stirred solution of 3-methyl-2-(methylaminomethyl)benzo[*b*]thiophene (0.30 g, 1.6 mmole) in 1:1 DMF/CH₂Cl₂ was added (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.33 g, 2 mmole), HOBt · H₂O (0.27 g, 2 mmole), and DCC (0.41 g, 2 mmole). The reaction was stirred for 16 hr, then was concentrated under vacuum. The residue was taken up in CHCl₃, washed with H₂O, dried (Na₂SO₄) and concentrated. Purification by flash chromatography on silica gel (4% methanol/CHCl₃) gave the title compound (0.39 g, 72%) as a pale yellow solid: LCMS (ES) *m/e* 338.2 (M + H)⁺.

15

Example 60

Preparation of (E)-3-(2-aminopyrimidin-5-yl)-N-(benzo[*b*]thiophen-2-ylmethyl)-N-methylacrylamide

20

According to the procedure of Example 1, except substituting (E)-3-(2-aminopyrimidin-5-yl)acrylic acid (1.49 g, 7.1 mmole) for (E)-3-(6-aminopyridin-3-yl)acrylic acid, and substituting 2-(methylaminomethyl)theino[2,3-*b*]thiophene (1.38 g, 7.8 mmole) for 1-methyl-2-(methylaminomethyl)indole, the title compound (2.04 g, 89%) was prepared as a yellow solid: MS (ES) *m/e* 325 (M + H)⁺.

25

Example 61

Preparation of (E)-3-(2-aminopyrimidin-5-yl)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide

30

According to the procedure of Example 31, except substituting 1-methyl-3-(methylaminomethyl)indole (1.96 g, 8.6 mmole) for 3-methyl-2-(methylaminomethyl)indene hydrochloride, and substituting 2-amino-5-bromopyrimidine

35

(1.0 g, 5.75 mmole) for 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one, the title compound (1.44 g, 78%) was prepared as a yellow solid: MS (ES) *m/e* 322 (M + H)⁺.

Example 62

5

Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 31, except substituting 1-methyl-3-(methylaminomethyl)indole (0.75 g, 3.3 mmole) for 3-methyl-2-(methylaminomethyl)indene hydrochloride, the title compound (0.59 g, 72%) was prepared as a light yellow solid: MS (ES) *m/e* 375 (M + H)⁺.

Example 63

15

Preparation of (E)-3-[2-aminopyrimidin-5-yl]-N-methyl-N-(3-methyl-1*H*-inden-2-ylmethyl)acrylamide

According to the procedure of Example 31, except substituting 2-amino-5-bromopyrimidine (0.32 g, 1.84 mmole) for 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one, the title compound (0.47 g, 80%) was prepared as a light yellow solid: MS (ES) *m/e* 321 (M + H)⁺.

Example 64

25

Preparation of (E)-3-[2-(acetylamino)pyrimidin-5-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

According to the procedure of Example 31, except substituting 1-methyl-2-(methylaminomethyl)indole (1.45 g, 8.33 mmole) for 3-methyl-2-(methylaminomethyl)indene hydrochloride, and substituting 2-acetylamino-5-bromopyrimidine (1.20 g, 5.55 mmole) for 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one, the title compound (2.38 g, 43%) was prepared as a yellow solid: MS (ES) *m/e* 364 (M + H)⁺.

35

Example 65Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(2-methyl-1H-indol-3-ylmethyl)acrylamide

5 According to the procedure of Example 1, except substituting 2-methyl-3-(methylaminomethyl)indole (0.45 g, 2.58 mmole) for 1-methyl-2-(methylaminomethyl)indole, the title compound (0.68 g, 90%) was prepared as a yellow solid: MS (ES) *m/e* 321 (M + H)⁺.

Example 66Preparation of (E)-3-(2-aminopyrimidin-5-yl)-N-(1,2-dimethyl-1H-indol-3-ylmethyl)-N-methylacrylamide

15 According to the procedure of Example 31, except substituting 1,2-dimethyl-3-(methylaminomethyl)indole (1.62 g, 8.62 mmole) for 3-methyl-2-(methylaminomethyl)indene hydrochloride, and substituting 2-amino-5-bromopyrimidine (1.00 g, 5.75 mmole) for 6-bromo-3,4-dihydro-1H-1,8-naphthyridin-2-one, the title
20 compound (1.33 g, 69%) was prepared as a yellow solid: MS (ES) *m/e* 336 (M + H)⁺.

Example 67Preparation of (E)-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)-3-(3-oxo-3,4-dihydro-2H-pyrido[3,2-*b*]-1,4-oxazin-7-yl)acrylamide

25 According to the procedure of Example 31, except substituting 1-methyl-2-(methylaminomethyl)indole (1.17 g, 6.75 mmole) for 3-methyl-2-(methylaminomethyl)indene hydrochloride, and substituting 5-bromo-2H-pyrido[3,2-*b*]-1,4-oxazin-3(4H)-one (1.03 g, 4.50 mmole) for 6-bromo-3,4-dihydro-1H-1,8-naphthyridin-2-one, the title compound (0.90 g, 53%) was prepared as a light yellow solid: MS (ES) *m/e*
30 377 (M + H)⁺.

Example 68Preparation of (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 31, except substituting 2-methyl-3-(methylaminomethyl)indole (1.40 g, 8.00 mmole) for 3-methyl-2-(methylaminomethyl)indene hydrochloride, the title compound (1.30 g, 65%) was prepared as a light yellow solid: MS (ES) *m/e* 376 (M + H)⁺.

Example 69Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl)acrylamide

According to the procedure of Example 31, except substituting 1-methyl-3-(methylaminomethyl)indole (0.38 g, 2.20 mmole) for 3-methyl-2-(methylaminomethyl)indene hydrochloride, and substituting 5-bromo-2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (0.32 g, 1.40 mmole) for 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one, the title compound (0.26 g, 50%) was prepared as a light yellow solid: MS (ES) *m/e* 377 (M + H)⁺.

Example 70Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)propionamide

To a solution of (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide (0.15 g, 0.40 mmole) in dioxane at RT was added Pd(OH)₂. The flask was sealed with a septum through which a balloon containing hydrogen (1 atm) was inserted. The reaction was stirred at RT overnight and then filtered through a pad of celite®, washing with methanol. The filtrate was concentrated to give the title compound (0.14 g, 94 %) as a light yellow solid: MS (ES) *m/e* 378 (M + H)⁺.

Example 71Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(6-methoxy-1-methyl-1H-indol-2-ylmethyl)-N-methylacrylamide

5

According to the procedure of Example 1, except substituting 1-methyl-2-(methylaminomethyl)-6-methoxy-1H-indole for 1-methyl-2-(methylaminomethyl)-1H-indole, the title compound (50%) was prepared as a light yellow solid: MS (ES) *m/e* 351.4 (M + H)⁺. Anal. Calcd for C₂₀H₂₂N₄O₂ · 1.5 H₂O: C, 63.64; H, 6.66; N, 14.84. Found:

10 C, 63.51; H, 6.21; N, 14.71.

Example 72Preparation of (E)-3-(7-aminopyridin-3-yl)-N-(1,7-dimethyl-1H-indol-3-ylmethyl)-N-methylacrylamide

15

According to the procedure of Example 1, except substituting 1,7-dimethyl-3-(methylaminomethyl)-1H-indole for 1-methyl-2-(methylaminomethyl)-1H-indole, the title compound (50%) was prepared as a light yellow solid: MS (ES) *m/e* 335.2 (M + H)⁺. Anal. Calcd for C₂₀H₂₂N₄O₂ · 0.5 H₂O: C, 69.99; H, 6.76; N, 16.31. Found: C, 70.02; H, 6.59; N, 16.43.

20

Example 73Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1,5-dimethyl-1H-indol-3-ylmethyl)-N-methylacrylamide

25

According to the procedure of Example 1, except substituting 1,5-dimethyl-3-(methylaminomethyl)-1H-indole for 1-methyl-2-(methylaminomethyl)-1H-indole, the title compound (33%) was prepared as a light yellow solid: MS (ES) *m/e* 335.2 (M + H)⁺. Anal. Calcd for C₂₀H₂₂N₄O₂ · H₂O: C, 68.16; H, 6.86; N, 15.89. Found: C, 68.37; H, 6.70; N, 15.62.

30

Example 74Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1,6-dimethyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

5

According to the procedure of Example 1, except substituting 1,6-dimethyl-3-(methylaminomethyl)-1*H*-indole for 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound (33%) was prepared as a light tan solid: MS (ES) *m/e* 335.2 (M + H)⁺. Anal. Calcd for C₂₀H₂₂N₄O₂ · 0.375 H₂O: C, 70.41; H, 6.64; N, 16.42. Found: C, 70.40; H, 10 6.61; N, 16.19.

Example 75Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1-benzyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

15

EDC (0.42 g, 2.20 mmole) was added to a solution of 3-(6-aminopyridin-3-yl)acrylic acid (0.36 g, 2.20 mmole), 1-benzyl-3-(methylaminomethyl)-1*H*-indole (0.50 g, 2.00 mmole), HOBT · H₂O (0.30 g, 2.20 mmole) and diisopropylethylamine (0.70 mL, 4.00 20 mmole) in DMF (30 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Flash chromatography on silica gel (10% MeOH/CHCl₃) gave the title compound (0.48 g, 60%) as a light yellow solid: MS (ES) *m/e* 397 (M + H)⁺.

25

Example 76Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(phenylamino)pyridin-3-yl]acrylamide

30

a) N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

To a stirred solution of 1-methyl-2-(methylaminomethyl)-1*H*-indole (1.5 g, 8.6 mmole) and Et₃N (1.35 mL, 9.6 mmole) in CH₂Cl₂ (75 mL) at 0 °C was added dropwise acryloyl chloride (0.77 mL, 9.5 mmole) over 5 minutes. After 2 h the reaction was washed 35 with cold H₂O, brine, dried (MgSO₄) and concentrated under vacuum. The residue was used without further purification.

b) (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(phenylamino)pyridin-3-yl]acrylamide

N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (from Example 76 (a))
5 was taken up in propionitrile (50 mL). To this solution was added with stirring 2-phenylamino-5-bromopyridine (1.3 g, 5.2 mmole), DIEA (1.8 mL, 10 mmole), Pd(OAc)₂ (112 mg, 0.5 mmole) and P(*o*-tol)₃ (304 mg, 1.0 mmole). The reaction was purged with argon then stirred at reflux for 16 h. After cooling to room temperature the reaction was concentrated to dryness under vacuum. Flash chromatography on silica gel (5%
10 methanol/CHCl₃) followed by a second flash column on silica gel (50-70% EtOAc/CHCl₃) left a residue that was triturated with EtOAc/petroleum ether. Filtration and drying under vacuum gave the title compound (1.42 g, 69%) as an off-white powder: MS (ES) *m/e* 396.20 (M + H)⁺.

15 Example 77

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1,2-dimethyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

20 To a stirred solution of 1,2-dimethyl-3-(methylaminomethyl)-1*H*-indole (0.8 g, 4.2 mmole) in 1:1 DMF/CH₂Cl₂ (30 mL) at RT was added (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.7 g, 4.3 mmole), Et₃N (0.61 mL, 4.3 mmole), HOBt · H₂O (0.58 g, 4.3 mmole) and EDC (0.83 g, 4.3 mmole). After 16 h the reaction was concentrated under vacuum and the residue was taken up in EtOAc (100 mL). The solution was washed with 1.0 N Na₂CO₃
25 (100 mL) then with brine, dried (Na₂SO₄), and concentrated. Purification by flash chromatography on silica gel (4% MeOH/CHCl₃) followed by trituration with 1:1 Et₂O/petroleum ether and drying under vacuum gave the title compound (1.36 g, 97%) as an off-white solid: MS (ES) *m/e* 335.2 (M + H)⁺.

30 Example 78

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(benzo[*b*]thiophen-3-ylmethyl)-N-methylacrylamide

35 According to the procedure of Example 77, except substituting 3-(methylaminomethyl)benzo[*b*]thiophene (0.75 g, 4.2 mmole) for the 1,2-dimethyl-3-

(methylaminomethyl)-1*H*-indole, the title compound (1.05 g, 83%) was prepared as an off-white solid: MS (ES) *m/e* 324.2 (M + H)⁺.

Example 79

5

Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(pyridin-2-ylamino)pyridin-3-yl]acrylamide

According to the procedure of Example 76 (a) and (b), except substituting 5-bromo-2,2'-dipyridylamine (1.3 g, 5.2 mmole) for the 2-phenylamino-5-bromopyridine, the
10 title compound (1.54 g, 75%) was prepared as an off-white solid: MS (ES) *m/e* 398.2 (M + H)⁺.

Example 80

15

Preparation of (E)-N-(1,2-dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

a) N-Methyl-N-(1,2-dimethyl-1*H*-indol-2-ylmethyl)acrylamide

20

According to the procedure of Example 76 (a), except substituting 1,2-dimethyl-3-(methylaminomethyl)-1*H*-indole (1.5 g, 8 mmole) for the 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound was prepared and used without further purification.

25 b) (E)-N-(1,2-Dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 76 (b), except substituting 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (1.3 g, 5.7 mmole) for the 2-phenylamino-5-bromopyridine, the title compound (0.57 g, 26%) was prepared as a white solid: MS (ES)
30 *m/e* 389.19 (M + H)⁺.

Example 81Preparation of (E)-N-methyl-N-(3-methylbenzo[*b*]thiophen-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

5

a) N-Methyl-N-(3-methylbenzo[*b*]thiophen-2-ylmethyl)acrylamide

According to the procedure of Example 76 (a), except substituting 2-(methylaminomethyl)-3-methylbenzo[*b*]thiophene (1.53 g, 8 mmole) for the 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound was prepared and used without further purification.

10

b) (E)-N-Methyl-N-(3-methylbenzo[*b*]thiophen-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 76 (b), except substituting 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (1.3 g, 5.7 mmole) for the 2-phenylamino-5-bromopyridine, the title compound (0.85 g, 33%) was prepared as an off-white solid: MS (ES) *m/e* 392.2 (M + H)⁺.

15

Example 82

20

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-(2-methylbenzo[*b*]thiophen-3-ylmethyl)acrylamide

According to the procedure of Example 77, except substituting 2-methyl-3-(methylaminomethyl)benzo[*b*]thiophene (1.2 g, 6.1 mmole) for the 1,2-dimethyl-3-(methylaminomethyl)-1*H*-indole, the title compound (1.22 g, 59%) was prepared as a pale yellow solid: MS (ES) *m/e* 338.2 (M + H)⁺.

25

Example 83

30

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(3,4-dimethylthieno[2,3-*b*]thiophen-2-ylmethyl)-N-methylacrylamide

According to the procedure of Example 1, except substituting 3,4-dimethyl-2-(methylaminomethyl)thieno[2,3-*b*]thiophene (0.026 g, 0.126 mmole) for the 1-methyl-2-

35

(methylaminomethyl)-1*H*-indole, the title compound (0.013 g, 72%) was prepared as a white solid: MS (ES) *m/e* 358 (M + H)⁺.

Example 84

5

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methylnaphthalen-2-ylmethyl)acrylamide

According to the procedure of Example 1, except substituting 1-methyl-2-(methylaminomethyl)naphthalene (0.100 g, 0.54 mmole) for the 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound (0.088 g, 49%) was prepared as a white solid: MS (ES) *m/e* 332 (M + H)⁺.

Example 85

15

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)acrylamide

According to the procedure of Example 1, except substituting 1-methyl-3-(methylaminomethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (0.2 g, 1.14 mmole) for the 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound (0.19 g, 52%) was prepared as a white solid: MS (ES) *m/e* 322 (M + H)⁺.

Example 86

25

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(2,3-dihydro-1*H*-3a-azacyclopenta[*a*]inden-8-yl)-N-methylacrylamide

According to the procedure of Example 1, except substituting 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene (0.100 g, 0.5 mmole) for the 1-methyl-2-(methylaminomethyl)-1*H*-indole, the title compound (0.063 g, 36%) was prepared as a white solid: MS (ES) *m/e* 347 (M + H)⁺.

Example 87Parenteral Dosage Unit Composition

5 A preparation which contains 20 mg of the compound of Example 1 as a sterile dry powder is prepared as follows: 20 mg of the compound is dissolved in 15 mL of distilled water. The solution is filtered under sterile conditions into a 25 mL multi-dose ampoule and lyophilized. The powder is reconstituted by addition of 20 mL of 5% dextrose in water (D5W) for intravenous or intramuscular injection. The dosage is thereby determined by the injection volume. Subsequent dilution may be made by addition of a metered volume of
10 this dosage unit to another volume of D5W for injection, or a metered dose may be added to another mechanism for dispensing the drug, as in a bottle or bag for IV drip infusion or other injection-infusion system.

Example 88

15

Oral Dosage Unit Composition

A capsule for oral administration is prepared by mixing and milling 50 mg of the compound of Example 1 with 75 mg of lactose and 5 mg of magnesium stearate. The resulting powder is screened and filled into a hard gelatin capsule.

20

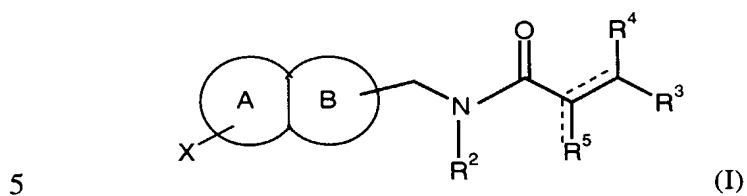
Example 89Oral Dosage Unit Composition

25 A tablet for oral administration is prepared by mixing and granulating 20 mg of sucrose, 150 mg of calcium sulfate dihydrate and 50 mg of the compound of Example 1 with a 10% gelatin solution. The wet granules are screened, dried, mixed with 10 mg starch, 5 mg talc and 3 mg stearic acid; and compressed into a tablet.

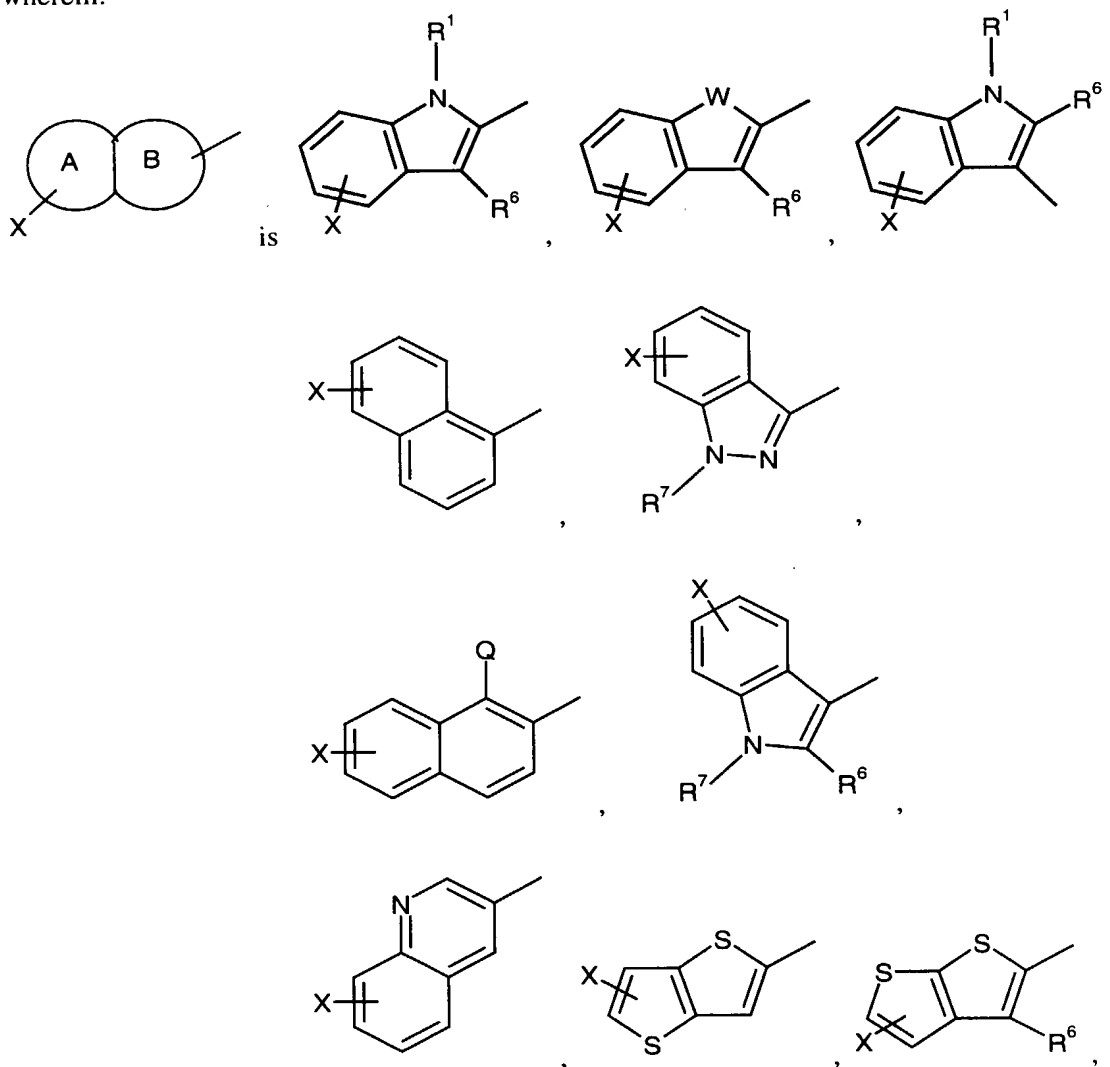
30 The above description fully discloses how to make and use the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprises the state of the art and are incorporated herein by reference as though fully set forth.

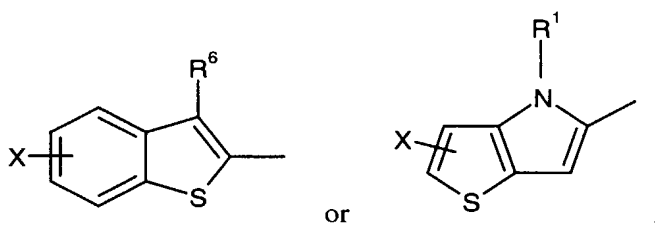
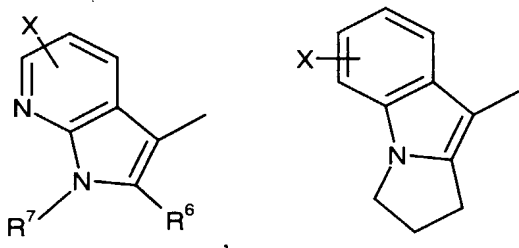
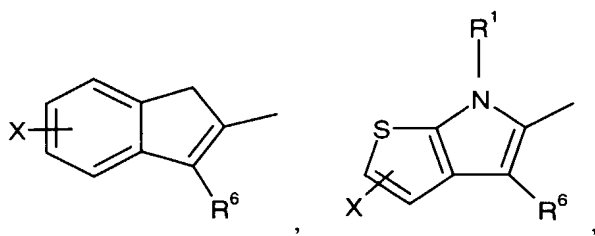
What is claimed is:

1. A compound according to formula (I):



wherein:





5

or

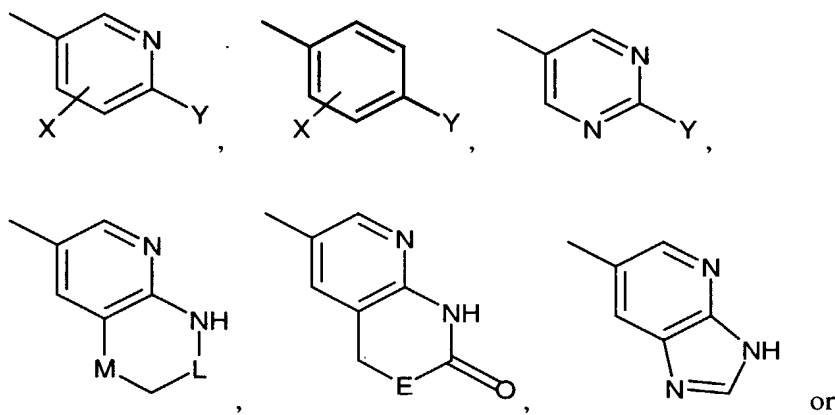
;

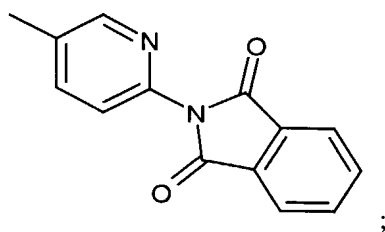
R^1 is H or C_{1-4} alkyl;

R^2 is H, C_{1-4} alkyl or C_{3-6} cycloalkyl;

R^3 is

10





R^4 is H or C_{1-4} alkyl;



indicates that one of the two designated bonds is a double bond and the other is a single bond;

5 R^5 is CH_2 when the bond to which it is attached is a double bond; or R^5 is H or C_{1-4} alkyl when the bond to which it is attached is a single bond;

R^6 is H or C_{1-4} alkyl;

R^7 is H, C_{1-6} alkyl or $-C_{0-6}$ alkyl-Ar;

Y is H, C_{1-4} alkyl, $N(R')_2$, $NHC(O)R'$, $NHCH_2C(O)R'$ or $NHC(O)CH=CHR'$;

10 each X independently is H, C_{1-4} alkyl, CH_2OH , OR' , SR' , CN, $N(R')_2$, $CH_2N(R')_2$, NO_2 , CF_3 , CO_2R' , $CON(R')_2$, COR' , $NR'C(O)R'$, F, Cl, Br, I or $-S(O)_rCF_3$;

W is S or O;

Q is H or C_{1-4} alkyl;

M is CH_2 or O;

15 L is CH_2 or $C(O)$;

E is O or NR' ;

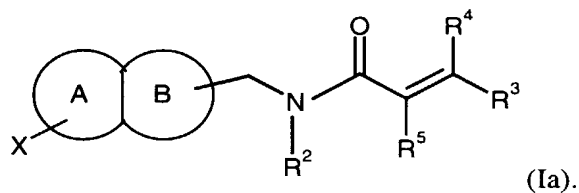
each R' independently is H, C_{1-6} alkyl or $-C_{0-6}$ alkyl-Ar; and

r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

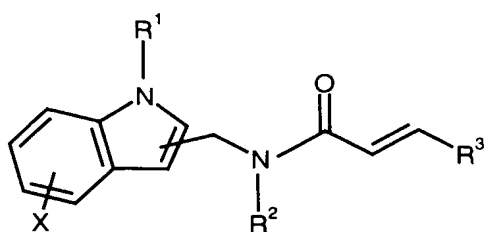
20

2. A compound according to claim 1 of formula (Ia):



25

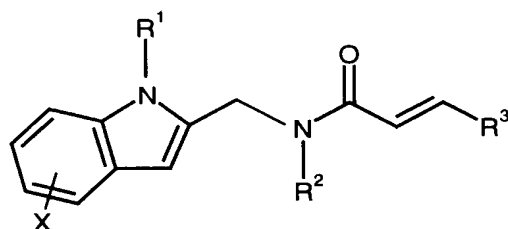
3. A compound according to claim 2 of formula (II):



(II).

4. A compound according to claim 1 of formula (IIa):

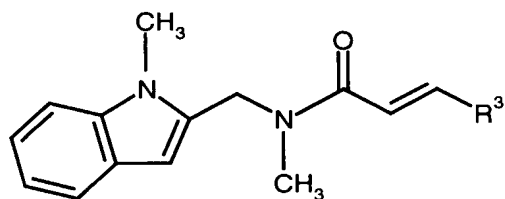
5



(IIa).

5. A compound according to claim 1 of formula (IIb):

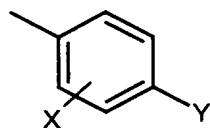
10



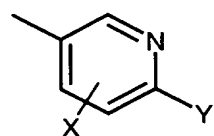
(IIb).

6. A compound according to claim 1 in which R³ is:

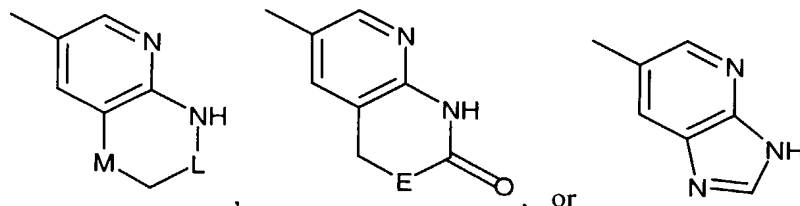
15



7. A compound according to claim 1 in which R³ is:



8. A compound according to claim 1 in which R³ is:



5

9. A compound according to claim 1 which is:

- (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-3-(4-Aminophenyl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- 10 (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(pyridin-3-yl)acrylamide;
- (E)-3-(2-Aminopyrimidin-5-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-(benzo[*b*]thiophen-2-ylmethyl)-N-methylacrylamide;
- 15 (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-2-butenamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indazol-3-ylmethyl)acrylamide;
- (E)-3-(6-Amino-2-methylpyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- 20 (E)-3-(6-Amino-5-methylpyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-(1-methyl-1*H*-indol-2-ylmethyl)-N-propylacrylamide;
- 25 (E)-3-(6-Aminopyridin-3-yl)-N-(5-fluoro-1-methyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(naphthalen-1-ylmethyl)acrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-2,N-dimethyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- 30 (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(naphthalen-2-ylmethyl)acrylamide;
- 2-(6-Aminopyridin-3-ylmethyl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-(benzofuran-2-ylmethyl)-N-methylacrylamide;

- (E)-3-(3,4-Dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl)-N-methyl-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-N-Methyl-3-[6-(methylamino)pyridin-3-yl]-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- 5 (E)-3-[6-(Dimethylamino)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-N-Methyl-N-[(1-methyl-1*H*-indol-2-yl)methyl]-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-3-[6-(Acetylamino)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- 10 (E)-3-(6-Amino-5-methylpyridin-3-yl)-N-(benzo[*b*]thiophen-2-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-Amino-5-methylpyridin-3-yl)-N-methyl-N-(naphthalen-2-ylmethyl)acrylamide;
- 15 (E)-3-(6-Amino-4-methylpyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-cyclopropyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide;
- 20 (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(quinolin-3-ylmethyl)acrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(thieno[2,3-*b*]thiophen-2-ylmethyl)acrylamide;
- (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(6-methylpyridine-3-yl)acrylamide;
- 25 (E)-3-[6-(Acetylamino)-5-methylpyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-(1*H*-indol-2-ylmethyl)-N-methylacrylamide;
- (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(2-oxopropylamino)pyridin-3-yl]acrylamide;
- 30 (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(thieno[3,2-*b*]thiophen-2-ylmethyl)acrylamide;
- (E)-3-[6-Amino-5-(hydroxymethyl)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- 35 (E)-3-(3*H*-Imidazo[4,5-*b*]pyridin-6-yl)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;

- (E)-3-[6-Aminopyridin-3-yl]-N-(1-ethyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide;
- (E)-3-[6-Aminopyridin-3-yl]-N-(1,3-dimethyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide;
- 5 (E)-3-[6-((E)-But-2-enoylamino)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-3-[6-Amino-5-[(2-hydroxyethylamino)carbonyl]pyridin-3-yl]-N-(1-methyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide;
- 10 (E)-3-[6-Aminopyridin-3-yl]-N-methyl-N-(3-methyl-1*H*-inden-2-ylmethyl)acrylamide;
- (E)-3-[6-Aminopyridin-3-yl]-N-(1*H*-inden-2-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(6-methyl-6*H*-thieno[2,3-*b*]pyrrol-5-ylmethyl)acrylamide;
- 15 (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]-1,3-oxazin-6-yl)acrylamide;
- (E)-3-[6-(1,3-dioxo-1,3-dihydroisindol-2-yl)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- 20 (E)-3-[6-[(2-Carboxybenzoyl)amino]pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-3-[6-(3-Ethylureido)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (E)-N-(1,3-Dimethyl-1*H*-indol-2-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 25 (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(3-methylbenzo[*b*]thiophen-2-ylmethyl)acrylamide;
- (E)-3-(6-Aminopyridin-3-yl)-N-(4-methoxy-1-methyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide;
- 30 (E)-3-[6-(Acetylamino)pyridin-3-yl]-N-methyl-N-(3-methyl-1*H*-inden-2-ylmethyl)acrylamide;
- (E)-3-[6-(Acetylamino)pyridin-3-yl]-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide;
- (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)acrylamide;
- 35 (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(propionylamino)pyridin-3-

- yl]acrylamide;
(E)-3-(6-Aminopyridin-3-yl)-N-(1,4-dimethyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide;
(E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(3-methylureido)pyridin-3-yl]acrylamide;
5 (E)-N-Methyl-N-(3-methyl-1*H*-inden-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
(E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(4-methyl-4*H*-theino[3,2-*b*]pyrrol-5-ylmethyl)acrylamide;
10 (E)-3-(6-Aminopyridin-3-yl)-N-(3,4-dimethylthieno[2,3-*b*]thiophen-2-ylmethyl)-N-methylacrylamide;
(E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(phenylamino)pyridin-3-yl]acrylamide;
(E)-3-(6-Aminopyridin-3-yl)-N-(6-methoxy-1-methyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide;
15 (E)-3-(2-Aminopyrimidin-5-yl)-N-(benzo[*b*]thiophen-2-ylmethyl)-N-methylacrylamide;
(E)-3-(2-Aminopyrimidin-5-yl)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide;
20 (E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(1-methylnaphthalen-2-ylmethyl)acrylamide;
(E)-3-(6-Aminopyridin-3-yl)-N-(1,2-dimethyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
(E)-3-(6-Aminopyridin-3-yl)-N-(benzo[*b*]thiophen-3-ylmethyl)-N-methylacrylamide;
25 (E)-N-Methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
(E)-3-[2-Aminopyrimidin-5-yl]-N-methyl-N-(3-methyl-1*H*-inden-2-ylmethyl)acrylamide;
30 (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(pyridin-2-ylamino)pyridin-3-yl]acrylamide;
(E)-3-[2-(Acetylamino)pyrimidin-5-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
(E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide;
35 (E)-3-(2-Aminopyrimidin-5-yl)-N-(1,2-dimethyl-1*H*-indol-3-ylmethyl)-N-

methylacrylamide;

(E)-N-(1,2-Dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;

(E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl)acrylamide;

(E)-N-Methyl-N-(3-methylbenzo[*b*]thiophen-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;

(E)-3-(6-Aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)acrylamide;

(E)-3-(6-Aminopyridin-3-yl)-N-(1,7-dimethyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;

(E)-3-(6-Aminopyridin-3-yl)-N-(1,5-dimethyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;

(E)-N-Methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;

(E)-3-(6-Aminopyridin-3-yl)-N-(1,6-dimethyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;

(E)-3-(6-Aminopyridin-3-yl)-N-(2,3-dihydro-1*H*-3a-azacyclopenta[*a*]inden-8-yl)-N-methylacrylamide;

(E)-3-(6-Aminopyridin-3-yl)-N-methyl-(2-methylbenzo[*b*]thiophen-3-ylmethyl)acrylamide;

(E)-3-(6-Aminopyridin-3-yl)-N-(1-benzyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;

(E)-N-Methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-(3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl)acrylamide; or

(E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)propionamide;

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition which comprises a compound according to claim 1 and a pharmaceutically acceptable carrier.

11. A method for inhibiting Fab I which comprises administering to a subject in need thereof a compound according to claim 1.

12. A method for inhibiting Fab K which comprises administering to a subject in need thereof:

(E)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide; or

- 5 (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
or a pharmaceutically acceptable salt thereof.

13. A method of treating bacterial infections which comprises administering to
10 a subject in need thereof a compound according to claim 1.

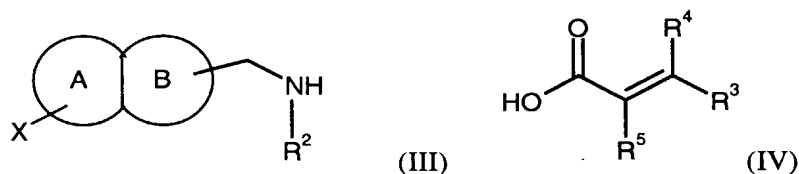
14. A compound according to any one of claims 1 to 9 for use as a medicament.

15 15. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of bacterial infections.

16. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases in which inhibition of Fab I is
20 indicated.

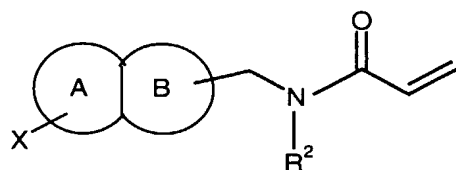
17. The use of (E)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide or (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide in the
25 manufacture of a medicament for the treatment of diseases in which inhibition of Fab K is indicated.

18. A process for preparing compounds of formula (I) as defined in claim 1, which process comprises:
30 (i) reacting a compound of formula (III) with a compound of formula (IV):



wherein R^2 , R^3 , R^4 , R^5 and X are as defined in formula (I), with any reactive functional groups protected, in the presence of EDC and HOBT;

(ii) reacting a compound of formula (V) with a compound of formula (VI):



(V) Halo- R^3 (VI)

wherein R^2 , R^3 and X are as defined in formula (I) and Halo is Br, Cl, F or I, with any reactive functional groups protected, in the presence of a palladium (II) salt, a phosphine ligand and base;

10 and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

15 19. A process for preparing crotonoyl-ACP, which process comprises reacting crotonoyl CoA and apo-acyl carrier protein, in the presence of *S. pneumoniae* ACP synthase.

20. A method of screening for an inhibitor of Fab I or FabK which comprises:

- (i) providing a reaction mixture comprising Fab I or Fab K, crotonoyl-ACP and NADPH or NADH;
- 20 (ii) contacting a candidate compound to said reaction mixture; and
- (iii) detecting inhibition of Fab I or Fab K.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/27844

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/339, 256, 336, 338, 357, 337, 249, 299, 314, 303 ; 546/277.4, 281.1, 275.7, 284.1, 112, 167, 118; 544/333, 105

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN EXPRESS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database CAPLUS on STN, AN 1986:68547, STUETZ et al. "Synthesis and structure-activity relationships of naftifine-related allyamine antimycotics" Abstrct, J. Med. Chem. (1986), 29(1), 112-25, see entire abstract.	1, 2, 6, 10
X	Database CAPLUS on STN, AN 1991:428908, FUSE et al. "Preparation of cinnamamide derivatives as antihyperlipidemics" abstract, EP 407200 A1, 09 January 1991(1991.01.09), see entire abstract.	1-6, 10, 14
A	Database CAPLUS on STN, AN 1999:325910, ASLANIAN et al. "Preparation of phenylalkylimidazoles as H3 receptor antagonists" Abstract, WO 9924406 A1, 20 May 1999 (1999.05.20), see entire abstract.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 DECEMBER 2000

Date of mailing of the international search report

25 JAN 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer
Dorothy Lawrence Fox
JANE FAN

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/27844

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-18

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/27844

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

C07D 401/12, 405/12, 209/14, 215/38, 221/02, 265/36, 498/02, 471/02; A61K 31/495, 31/381, 31/4436, 31/4439, 31/47, 31/506, 31/5365

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/339, 256, 336, 338, 357, 337, 249, 299, 314, 303 ; 546/277.4, 281.1, 275.7, 284.1, 112, 167, 118; 544/333, 105

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-18, drawn to various organic compounds, their preparation, their composition and method of using the same.

Group II, claim(s) 19, drawn to a process of preparing crotonoyl-ACP in the presence *S. pneumoniae* ACP synthase.

Group III, claim(s) 20, drawn to a method of screening for an inhibitor of Fab I or FabK.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: similar compounds have other uses, such as antifungal agents besides for the preparation of crotonoyl-ACP. Note

CA104:68547.